Progress in Neurobiology 156 (2017) 69–89

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

Old and new challenges in Parkinson's disease therapeutics

Ana O. Pires[a,b], F.G. Teixeira[a,b], B. Mendes-Pinheiro[a,b], Sofia C. Serra[a,b], Nuno Sousa[a,b], António J. Salgado[a,b,*]

[a] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal
[b] ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal

ARTICLE INFO

Article history:
Received 25 May 2015
Received in revised form 15 March 2017
Accepted 20 April 2017
Available online 27 April 2017

Keywords:
Parkinson's disease
Pathophysiology
Cell therapy
Gene therapy
Molecular therapy
Clinical trials
Mesenchymal stromal/stem cells
Secretome

ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the degeneration of dopaminergic neurons and/or loss od neuronal projections, in several dopaminergic networks. Current treatments for idiopathic PD rely mainly on the use of pharmacologic agents to improve motor symptomatology of PD patients. Nevertheless, so far PD remains an incurable disease. Therefore, it is of utmost importance to establish new therapeutic strategies for PD treatment. Over the last 20 years, several molecular, gene and cell/stem-cell therapeutic approaches have been developed with the aim of counteracting or retarding PD progression. The scope of this review is to provide an overview of PD related therapies and major breakthroughs achieved within this field. In order to do so, this review will start by focusing on PD characterization and current treatment options covering thereafter molecular, gene and cell/stem cell-based therapies that are currently being studied in animal models of PD or have recently been tested in clinical trials. Among stem cell-based therapies, those using MSCs as possible disease modifying agents for PD therapy and, specifically, the MSCs secretome contribution to meet the clinical challenge of counteracting or retarding PD progression, will be more deeply explored.

Contents

Abbreviations: 6-OHDA, 6-hydroxydopamine; AADC, aromatic amino acid decarboxylase; AAV, adeno-associated virus; ADX88178, 5-methyl-N-(4-methylpyrimidin-2-yl)-4-(1H-pyrazol-4-yl)thiazol-2amine; ASCs, adipose stem/stromal cells; BDNF, brain-derived neurotrophic factor; BMSCs, bone marrow mesenchymal stem/stromal cells; CD, cluster of differentiation 11b; CO, cross-over; COMT, cathecol-O-methyltransferase; DA, dopamine; DAergic, dopaminergic; DB, double-blind; DBS, deep brain stimulation; DS, delayed start; ES cells, embryonic stem cells; FDA, Food and drug administration; FVM, fetal ventral mesencephalic; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; GDNF, glial cell-derived neurotrophic factor; GFs, growth factors; GPi, internal globus pallidus; iN cells, induced neural cells; iPS cells, induced pluripotent stem cells; L-DOPA, levodopa; LSP1-2111,, (2S)-2-amino-4-[hydroxy[hydroxy(4-hydroxy-3-methoxy-5-nitro phenyl)methyl]phosphoryl]butanoic acid; MC, multicenter; MD, multi-dosage; mGluR4, metabotropic glutamate receptor 4; miRNA, micro-ribonucleic acid; mRNA, messenger ribonucleic acid; MSCs, mesenchymal stromal/stem cells; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NCT, National clinical trial; NSCs, neural stem cells; NTN, neurturin; PC, placebo controlled; PD, Parkinson's disease; PG, parallel group; PHCCC, *N*-phenyl-7-(hydroxylimino)cyclopropa[*b*]chromen-1a-carboxamide; RD, randomized; SNpc, substantia nigra *pars compacta*; STN, subthalamic nucleus; TH, tyrosine hydroxylase; UKPDBB, United Kingdom parkinson's disease society brain bank; VU0155041, (+/−)-cis-2-(3,5-dichlorphenylcarbamoyl)cyclohexanecarboxylic acid; WJ-MSCs, Wharton's jelly mesenchymal stem cells.

* Corresponding author at: Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal.
E-mail addresses: anapiresm@med.uminho.pt (A.O. Pires), fabioteixeira@med.uminho.pt (F.G. Teixeira), barbaramp@med.uminho.pt (B. Mendes-Pinheiro), njcsousa@med.uminho.pt (N. Sousa), asalgado@med.uminho.pt (A.J. Salgado).

http://dx.doi.org/10.1016/j.pneurobio.2017.04.006
0301-0082/

1. Introduction

Parkinson's disease (PD) is the most common motor-related disorder in middle or late life, affecting millions worldwide (Pereira and Aziz, 2006). It was first described in 1817 by James Parkinson on his original "An essay on the shaking palsy" as "paralysis agitans", after observing signs of tremor, festinating gait and flexed posture in six patients (Parkinson, 1817; Pereira and Aziz, 2006). "Paralysis agitans" was later named "maladie de Parkinson" or Parkinson's disease in 1888 by Charcot (Charcot, 2002). The scope of this review is to provide an overview on PD and related therapies, including the most recent trends within this field. For that, it will first characterize PD and will focus thereafter on clinical features and diagnosis, as well as on current clinical approaches and emerging molecular and stem cell-based therapies, particularly those using mesenchymal stem cells (MSCs). An overview of new candidate drugs and the current status of gene therapy for PD treatment will also be provided. All the therapeutic approaches outlined in this review aiming at treating the motor symptoms of PD are summarized in Fig. 1.

2. Parkinson's disease

Parkinson's disease is a slowly progressive neurodegenerative disease, primarily characterized by the increasing loss of dopaminergic (DAergic) neurons. This happens in several dopaminergic networks (mesocortical, mesolimbic and nigro-striatal pathways), presenting a stronger impact in the ventral tier of the substantia nigra *pars compacta* (SNpc) within the mesostriatal/nigrostriatal pathway (Cummins and Barker, 2012; Koller, 2003; Pereira and Aziz, 2006; Teixeira et al., 2013). Loss of substantia nigra (SN) neurons leads to less DAergic innervations and consequently to striatal dopamine (DA) deficiency, the main responsible for most of the sensory-motor symptoms of PD (Dauer and Przedborski, 2003).

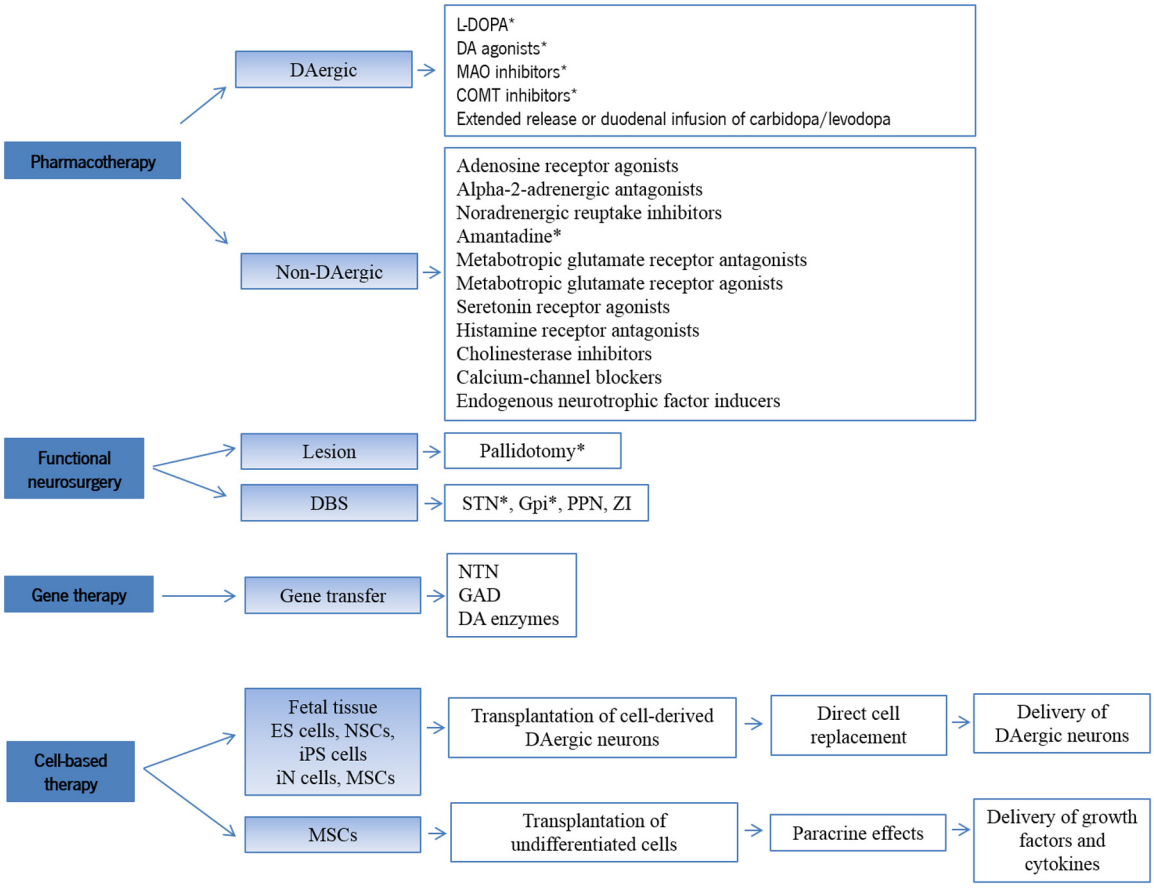

Fig. 1. Summary of PD therapeutic approaches currently used in clinics or under research (* indicates current therapeutic approaches used in clinics).

By the time PD motor symptoms appear, approximately 60% of DAergic neurons in SN and 80% of striatal DA terminals have already been lost (Beach et al., 2008; Cheng et al., 2010; Dauer and Przedborski, 2003; Nandhagopal et al., 2008). Although the etiology of SN degeneration is unknown, in addition to the motor symptomatology, the presence of Lewy bodies (LBs) is another hallmark feature of PD and is typically used as a post-mortem confirmation of the disease (Olanow and Brundin, 2013). LBs are distinctive intracytoplasmatic inclusions, containing a variety of cellular proteins, being α-synuclein the most abundant one (Benskey et al., 2016). The precise reason why LBs form and its role in pathogenesis of PD remains undetermined (Dickson et al., 2009). However, in recent years, it has become clear that the initial sites displaying LBs are the dorsal motor nucleus of the vagus in the brainstem and the olfactory bulb, which is described as stage I of the disease. This staging was firstly proposed by Braak and colleagues (Braak et al., 2003a), demonstrating that the disease most likely progresses in an upward direction via the pons (stage II) to the midbrain (stage III), followed by the basal prosencephalon and mesocortex (stage IV), and eventually reaching the temporal cortex and neocortex (stages V and VI) (Braak et al., 2003b). However, it is only at stage III, when DAergic neuronal death and striatal nerve terminals exceed a critical threshold (as mentioned above) that motor features of PD become evident. This means that there is a substantial pre-symptomatic period when the disease is hidden possibly due to the existence of compensatory mechanisms (Navntoft and Dreyer, 2016).

There has been converging evidence suggesting that PD can start in the gut, before spreading to the olfactory bulb and caudal brainstem and then progressing through the brainstem and the diencephalon until it eventually reaches the cortex (Jankovic, 2016). Based on this idea, Gjerløff and colleagues (Gjerloff et al., 2015) proposed that in addition to the loss in dopaminergic innervation, catecholaminergic and cholinergic neurons are also vulnerable and affected on PD (Gjerloff et al., 2015). Through an imaging acetylcholinesterase (AChE) density of the peripheral organs using positron emission tomography (PET), these authors found not only loss of cholinergic innervation in the gastrointestinal tract, but also that the pancreas seems to be affected, since it receives innervation from the dorsal vagal motor nucleus (DMV). However, no studies have yet analyzed histologically the distribution of cholinergic markers in PD patient's pancreas, thereby raising the question about which structures within it exhibit the decreased AChE expression and if this could be used as a biomarker or a diagnostic strategy for PD (Gjerloff et al., 2015).

Approximately 5–10% of patients present the classical Mendelian inheritance form of PD ("familial PD"), with patients presenting mutations in the genes that have been related to neurodegeneration (*e.g.*, α-synuclein, parkin, tau and ubiquitin c-terminal hydrolase) (Bras and Singleton, 2009; Dexter and Jenner, 2013; Simon-Sanchez et al., 2009). In spite of that, the most common form of PD is sporadic. It is believed that the interaction of multiple genetic susceptibilities and environmental factors underlie the cause for this idiopathic form of PD (Dawson and Dawson, 2003; Di Monte, 2003). In addition, biochemical abnormalities such as mitochondrial dysfunction, free radical mediated damage, excitotoxicity, inflammatory change and proteasomal dysfunction have also been reported to mediate PD pathogenesis (Dauer and Przedborski, 2003; Schapira, 2005). Although it is well known that DAergic neuronal loss is severe in the SNpc at later stages of PD, there is a lack of information regarding the rate and magnitude of this degeneration in the different stages of the disease, particularly in the early stages after diagnosis. Indeed, Kordower and colleagues (Kordower et al., 2013) have recently supported this idea, proposing that such information may be crucial for understanding the natural evolution of PD. By performing a correlation between disease duration and integrity of the nigrostriatal system, these authors found that although PD progresses beyond the first decade, the phenotypic changes in the nigrostriatal pathway are greater than the structural changes. This suggests that the clinical dysfunction that is observed is likely due to a severe loss of function of the nigrostriatal neurons (Kordower et al., 2013), which may be due to a degeneration of the DAergic terminals and not its loss, thereby indicating that possibly DAergic neurons may be dysfunctional but still potentially viable and recoverable. Nevertheless, answers to these observations require additional studies and tools, particularly in early stages of the disease where there is a greater chance that surviving/viable DAergic neurons benefit from therapy.

2.1. Parkinson's disease clinical features

PD clinical features include a variety of motor and non-motor symptoms. Since there are no definitive diagnostic tests for this disease and it may often be confused with other parkinsonian disorders (*e.g.*, essential tremor, multiple system atrophy and progressive supranuclear palsy), clinicians require thorough knowledge of PD clinical manifestations to differentiate it from other conditions. The discovery of new biomarkers specific for PD could obviate this problem in the future.

From the motor point of view, PD is characterized by the appearance of motor cardinal features namely bradykinesia, resting tremor, rigidity, and postural instability (Jankovic, 2008; Koller, 2003; Massano and Bhatia, 2012). At the onset of the disease, patients typically present asymmetrical tremors, more prominent in the upper extremities (Koller, 2003). As the disease progresses, patients are equally affected on both sides of the body, with bilateral bradykinesia becoming evident (Koller, 2003). Later on, patients reveal postural instability, gait dysfunctions (freezing and festination) and severe balance impairments, that frequently lead to falls (Koller, 2003). Bradykinesia or slowness of movement is the most characteristic clinical feature of PD (Jankovic, 2008), that manifests by difficulties in initiation, execution and arrest of movement, or in any task requiring fine motor control (Jankovic, 2008; Koller, 2003). Tremor at rest, particularly in distal part of the extremities, is also one of the most recognizable symptoms of PD (Jankovic, 2008). Additionally present postural tremor, may also represent a manifestation of PD (Jankovic, 2008; Koller, 2003). Rigidity is characterized by increased resistance to muscle stretch and relaxation, due to tightness and stiffness of muscles and may occur proximally (*e.g.*, neck, shoulders, hips), distally (*e.g.*, wrists, ankles) or both. It is often associated with pain (*e.g.*, painful shoulder) and, later in the disease, with postural deformities, such as flexed neck and trunk posture, as well as flexed elbows and knees (Jankovic, 2008; Koller, 2003). In later stages of PD, postural instability also becomes evident as a result of loss of postural reflexes. The latter is usually followed by freezing, a form of movement loss (akinesia) characterized by a sudden transient inability to move, contributing to loss of balance (postural instability) and subsequent falls (Giladi et al., 2001; Jankovic, 2008; Koller, 2003). Although freezing does not occur universally, it is probably the most disabling of all PD symptoms in more advanced stages. Finally, in certain circumstances, particularly in patients with postural instability and flexed truncal posture, festination of gait (involuntary quickening of gait) may also occur (Koller, 2003).

Although PD is generally considered a motor control disorder and the cardinal signs of the disease rely on motor disabilities, a variety of non-motor features also emerge due to the degeneration of other neuronal pathways (Koller, 2003). These non-motor features are commonly known as PD non-motor symptoms and are very frequent, contributing significantly for the morbidity and

impaired quality of life of the patients (Hely et al., 2005; Schapira, 2005; Shulman et al., 2001). They are characterized by neuropsychiatric, autonomic, sensory and sleep abnormalities (Jankovic, 2008; Koller, 2003; Schapira, 2005). The most frequent neuropsychiatric comorbidities include apathy (anhedonia), dementia, anxiety disorders (*e.g.*, panic attacks), depression, hallucinations, psychosis and impulse control disorders (*e.g.*, obsessive-compulsive and impulse behaviors) (Jankovic, 2008; Koller, 2003; Schapira, 2005). Autonomic/involuntary nervous system control dysfunctions affect about one third of PD patients (Koller, 2003). The most common autonomic abnormalities are orthostatic hypotension, sweating dysfunction, bowel problems, constipation, dysphagia (swallowing difficulties), sialorrhoea (excessive production of saliva), sphincter and erectile dysfunction (Jankovic, 2008; Koller, 2003; Schapira, 2005). Sensory disturbances also affect PD patients, but often pass unrecognized as parkinsonian disturbances (Koller, 2003; Shulman et al., 2002). These include anosmia (lack of olfaction), akathisia (physical restlessness and subjective urge to move), paresthesias (abnormal sensation of the skin like burning, prickling and formication) and pain (Jankovic, 2008; Koller, 2003). Finally, sleep disturbances such as excessive sleepiness, sleep attacks, insomnia as well as rapid-eye movement sleep behavior, are also common in PD (Gjerstad et al., 2006, 2007; Jankovic, 2008).

3. Current clinical therapies in Parkinson's disease

3.1. PD pharmacotherapies

The pioneer work of Carlsson and colleagues (1957) on the discovery of DA as a putative neurotransmitter (Björklund et al., 2010), together with the findings from Ehringer and Hornykiewicz (1960) which revealed that dopamine concentrations were markedly decreased in the striatum of PD patients (Ehringer and Hornykiewicz, 1998), paved the way for the use of L-DOPA in the clinical setting (Pandey, 2012; Smith et al., 2012). Indeed L-DOPA revolutionized the treatment of cardinal motor symptoms of PD (rest tremor, rigidity, bradykinesia and postural instability) leading to improved daily function, quality of life and survival of PD patients (Smith et al., 2012). Over the last decades, L-DOPA has become known as the "gold standard" therapy for PD motor symptoms. However, chronic use of L-DOPA often leads to motor fluctuations and drug-induced dyskinesias (Factor and Weiner, 2008; Schapira, 2005; Smith et al., 2012). The mechanisms underlying these effects are not completely understood, but are most likely related with the pulsatile stimulation of DA receptors and the degree of striatal denervation (Obeso et al., 2000; Schapira, 2005). In an attempt to solve these motor complications, dopamine receptor agonists started to be administrated, either alone or as combinatorial therapy with L-DOPA (Lang and Lees, 2002; Schapira, 2005; Smith et al., 2012). Nevertheless, the use of DA receptor agonists is not free from motor disturbances, often leading to major autonomic and psychiatric side effects that outweigh their beneficial effects in PD patients (Smith et al., 2012). Currently, two oral (pramipexole, ropinirole), and one injectable (apomorphine), DA receptor agonists are available for administration to these patients (Smith et al., 2012). They were developed to reduce prevalence of drug-induced dyskinesias in PD patients and their efficacy was later confirmed in large-scale randomized controlled trials (Dewey et al., 2001; Parkinson Study Group, 2000; Rascol et al., 2000). Besides having specific action in certain DA receptors subtypes, pramipexole and ropinirole have longer half-lives, which presumably avoids rapid fluctuations in DA receptors stimulation, thereby managing dyskinesias in such patients (Schapira, 2005; Smith et al., 2012). However, although pramipexole and ropinirole DA receptor agonists diminish the risk of dyskinesias in PD patients, they often generate major non-motor side effects like psychiatric symptoms (*e.g.*, hypomania, euphoria, paranoia, confusion, delusions, hallucinations), psychiatric disorders (*e.g.*, psychosis, depression, impulse control disorders), autonomic side effects (*e.g.*, orthostatic hypotension) and sleep disorders (Factor, 2008; Kalinderi et al., 2011; Olanow et al., 2009b;

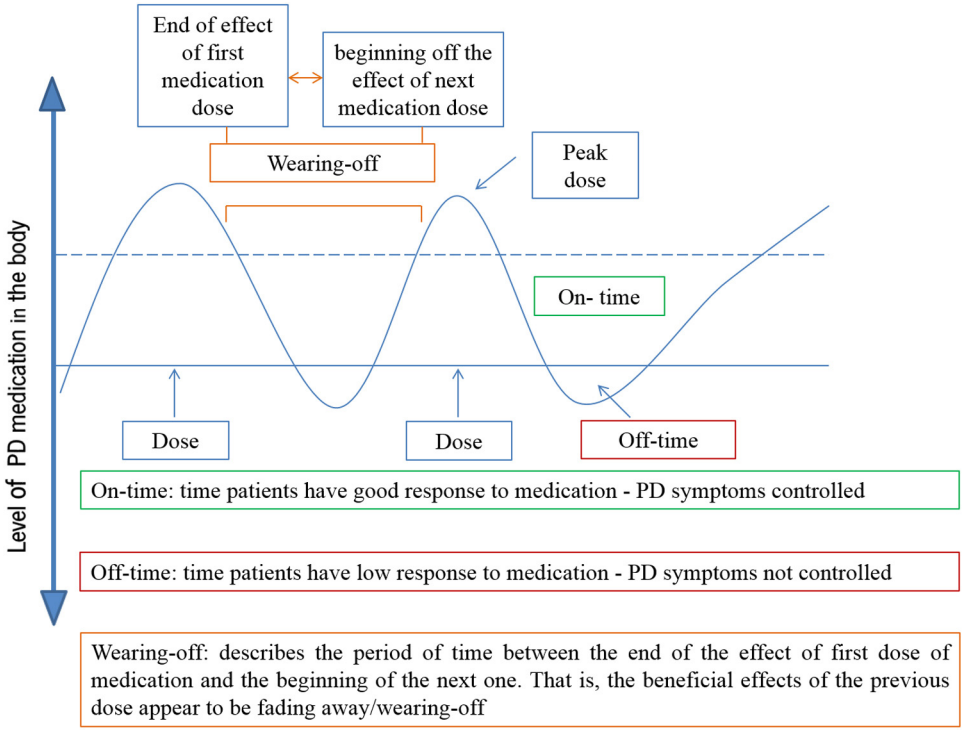

Fig. 2. Wearing-off typical pattern during the day in PD patients.

Smith et al., 2012). This means that, sooner or later, supplementation with L-DOPA will be required (Rascol et al., 2000; Schapira, 2005). Therefore, pramipexole and ropinirole are currently being administrated as monotherapy early in the course of PD, or in combination with L-DOPA in mid- to late-stages of the disease. On the other hand, apomorphine is one of the oldest non-ergot short-acting DA receptor agonists, with receptor affinity (D1, D2, D3) similar to the referred neurotransmitter (Factor, 2008; Smith et al., 2012). Apomorphine is also the only DA receptor agonist that has been shown to possess an anti-parkinsonian efficacy similar to L-DOPA in double-blinded clinical trials (Dewey et al., 2001; Koller, 2003; Smith et al., 2012). This similarity, together with the short-acting activity of apomorphine, may explain the appearance of autonomic side effects resembling those described for pramipexole and ropinirole, although with a lower prevalence of psychiatric problems (Dewey et al., 2001; Pfeiffer et al., 2007; Smith et al., 2012). The use of apomorphine for treating PD has been avoided for several years due to its emetic (vomit-inducing) action (Dewey et al., 2001; Koller, 2003). But the development of an injectable form (apomorphine hydrochloride) allowed to surpass these limitations and nowadays apomorphine is used as an adjuvant to other anti-parkinsonian medications (Dewey et al., 2001; Pfeiffer et al., 2007; Smith et al., 2012). In spite of its benefits, reported technical difficulties and cutaneous adverse effects, after long-term subcutaneous infusions, made this drug an unattractive choice for PD treatment (Smith et al., 2012). As consequence, injectable apomorphine is only used in unpredictable motor fluctuations (end-of-dose "wearing off") and "off" episodes in later stage PD patients (Koller, 2003) (Fig. 2).

Inhibitors of dopamine metabolizing enzymes like monoamine oxidase B (MAO-B), (peripheral) cathecol-O-methyltransferase (COMT) and aromatic L-aminoacid decarboxylase, are other agents presently used for normalizing DAergic transmission. In 1962, monoamine oxidase inhibitors were found to potentiate the anti-parkinsonian effect of L-DOPA (Bernheimer et al., 1962; Koller, 2003).

Currently, selegiline and rasagiline are the most common MAO-B inhibitors used in the treatment of PD (Peretz et al., 2016). Several clinical guidelines have been established, proposing the initiation of PD treatment with these drugs, in order to delay the introduction of L-DOPA (Connolly and Lang, 2014; Olanow et al., 2001). Indeed, the efficacy of both drugs has been widely supported (Jost et al., 2014). Stowe and colleagues (Stowe et al., 2011) suggested in their meta-analysis that selegiline and rasagiline have comparable effects in the treatment of PD. However, this assumption still remains under some controversy. Results from five studies with selegiline and four with rasagiline revealed similar effects in their treatment efficacy (Marconi and Zwingers, 2014). Nevertheless, in an indirect meta-analysis performed by Jost and colleagues (Jost et al., 2012), it was reported that rasagiline takes advantage over selegiline, when the UPDRS total score is used. Recently, Peretz and colleagues (Peretz et al., 2016) suggested some possible advantage for selegiline, either because of better symptomatic effects or superiority in its disease-modifying effects, when compared to rasagiline.

Altogether, results revealed that selegiline and rasagiline were effective in early stages of PD, leading to their current adoption as monotherapy in early stages of PD. On the other hand, they can also be used in combination with L-DOPA to reduce motor fluctuations and "off" episodes in advanced PD patients (Factor, 2008; Group, 2005a; Kalinderi et al., 2011; Olanow et al., 2008a, 2009a,b; Parkinson Study Group, 1989, 2002; Rascol et al., 2011). It is also worth mentioning that MAO-B inhibitors were suggested to act as neuroprotective agents (Akao et al., 2002; Bar Am et al., 2004; Jenner, 2004; Maruyama et al., 2002). However, their potential for displaying neuroprotective properties has been surrounded by controversy (Hart et al., 2009; Olanow et al., 2008a,b; Rascol, 2009). As reviewed by Knudsen Gerber (2011) both selegiline and rasagiline have been suggested to withhold neuroprotective properties. Still, for selegiline studies have yet to show a definitive conclusion (Fernandez and Chen, 2007). Meanwhile, the use of rasagiline in clinical studies also demonstrated a delayed and reduced need for future use of L-DOPA (Group, 2005a).

Inhibitors for COMT (*e.g.*, tolcapone, entacapone) and aromatic L-aminoacid decarboxylase (*e.g.*, carbidopa), have been developed to improve the L-DOPA therapeutic effect (Koller, 2003). Demonstration of COMT inhibitors (*e.g.*, antacapone, tolcapone) effectiveness in decreasing motor fluctuations in advanced PD patients, when combined with L-DOPA or with L-DOPA-carbidopa (Heikkinen et al., 2002; Larsen et al., 2003; Nutt et al., 1994; Parkinson Study Group, 1997; Poewe et al., 2002; Rinne et al., 1998; Schapira, 2005; Smith et al., 2012), led to FDA approval for their clinical use.

Anticholinergics are amongst the oldest class of pharmaceuticals used as therapeutic agents for the management of PD (Factor and Weiner, 2008; Koller, 2003; Smith et al., 2012). Considered the first treatment for PD, the effectiveness of anticholinergic treatments was postulated in the theory stating that the origin of PD motor symptoms was the result of an imbalance between acetylcholine and dopamine in the striatum (Aosaki et al., 2010; Kalinderi et al., 2011). However, over the years their use has declined, due to the introduction of L-DOPA and dopamine agonists (Aosaki et al., 2010). Nowadays, it is mainly clinically adopted for the treatment of young patients with PD-associated tremor or dystonia (Koller, 2003; Smith et al., 2012).

Amantadine is another FDA approved anti-parkinsonian agent. It acts by blocking glutamatergic hyperactivity, which has been associated with PD pathology (Rascol et al., 2011; Smith et al., 2012). It is the only ionotropic glutamate receptor antagonist that has been shown to have robust antidyskinetic properties in the reduction of L-DOPA-induced dyskinesias (Factor, 2008; Kalinderi et al., 2011; Olanow et al., 2009b; Smith et al., 2012). Therefore, it is the only drug currently used capable of concomitantly reduce dyskinesia and improve PD symptoms (Ferreira and Rascol, 2000; Koller, 2003).

A summary of study design and number of patients as well as primary outcome measure, main results and conclusions from trial studies above referenced is provided in Table 1.

3.2. PD surgical interventions

The first reports showing that surgery interventions within the basal ganglia could resolve tremor and rigidity came from the work published by Russel Meyers in 1942 and 1951 (Meyers, 1942, 1951). Following this, several groups conducted surgeries based in ablative techniques. At the time, surgical ablation was performed in different basal ganglia locations, such as the anterodorsal and posteriomedial segments of the pallidum (pallidotomy), as well as the ventrolateral and the ventral intermediate segments of the thalamus (thalamotomy) (Alexander et al., 1990; Jankovic et al., 1995; Koller, 2003). As a consequence of the reported benefits of this type of surgery in improving tremor and rigidity, ablative surgeries (pallidotomy, thalamotomy) became the standard procedure for treatment of PD motor symptoms between the 1950s and the 1960s (Pandey, 2012). In the 1960s, with the advent of L-DOPA as an effective drug for PD motor symptoms, surgery for PD gradually declined. However, several other events in the past twenty-five years contributed for the reemergence of neurosurgical interventions for PD management. For instance, reversible lesioning by deep brain stimulation (DBS), pioneered by Cooper in the early 1970s (Cooper, 1973; Pereira and Aziz, 2006), as well as the outcomes provided by non-human primate models of PD in understanding basal ganglia pathophysiology (Aziz et al., 1991;

Table 1
Summary of key clinical trials conducted using current drug options for treatment of PD patients' motor symptomatology.

References	Drug(s)	Study design	Patients	Nr. of subjects	Primary outcome measure	Results
Parkinson Study Group (1989) DATATOP study	Selegiline *vs.* Tocopherol	RD, DB, PC; 25 months	Early untreated	800	Extends the time until disability requires therapy with L-DOPA	Selegiline delayed the onset of L-DOPA therapy and slowed parkinsonism disability. Disease-modifying effects of selegiline were not found.
Nutt et al. (1994)	Entacapone + L-DOPA	Unblinded; 8 weeks	Advanced fluctuations	15	Effect of entacapone in L-DOPA pharmacokinetics and pharmacodynamics	The inhibition of COMT by entacapone decreases the plasma elimination of L-DOPA and enhances the antiparkinsonian effects of single and repeated doses of L-DOPA.
Parkinson Study Group (1997) SEESAW study	Entacapone + L-DOPA	MC, DB, PC, PG, MD; 24 weeks	Advanced fluctuations	205	Changes in "on" time	Entacapone is generally effective in subjects with motor fluctuations, extending the benefits of L-DOPA and ameliorating the symptoms of PD. Patients with the greatest amount of off-time periods are those who are most likely to benefit from this drug.
Rinne et al. (1998) Nordic NOMECOMT study	Entacapone + L-DOPA	RD, PC, DB, PG; 6 months	Advanced fluctuations	171	Changes in on-time and off-time periods	Long-term entacapone treatment effectively prolonged the effect of L-DOPA, increasing the on-time, and reducing the off-time and L-DOPA daily dosage; Increase in UPDRS scores.
Rascol et al. (2000) Part of 056 study	Ropinerole *vs.* L-DOPA	RD, DB, PG; 5 years	Early untreated	268	Occurrence of dyskinesias	The cumulative incidence in dyskinesias after 5 years follow-up was lower in ropinerole group when compared with L-DOPA alone. Adverse effects: higher incidence of hallucinations in ropinerole group and similar incidence of nausea among groups.
Parkinson Study Group (2000) CALM-PD study	Pramipexole *vs.* L-DOPA	MC, RD, DB, PG; 4 years	Early untreated	301	Time to occurrence of motor complications	Initial pramipexole treatment reduced the risk of developing motor complications, but was not as potent as L-DOPA in improving the parkinsonian features (measured by UPPERS). Adverse effects: somnolence, hallucinations, generalized and peripheral edema in patients treated with pramipexole.
Parkinson Study Group (2002) TEMPO study	Rasagiline	MC, RD, DB, PC, PG, MD; 26 weeks	Early untreated	404	Change in UPPERS (I, II, III, IV)	Rasagiline induced an increase in UPPERS III when compared to placebo treatment. Further studies are needed to evaluate rasagiline long-term effect.
Larsen et al. (2003) (extension of NOMECOMT study)	Entacapone + L-DOPA	RD, DB, PC, PG; 3 years	Advanced fluctuations	132	Change in off-time period	Entacapone increased the benefit of L-DOPA single dose and decreased the off-time period. Adverse effects: diarrhea, insomnia, dizziness, nausea, and hallucinations.
Group (2005a) PRESTO study	Rasagiline	MC, RD, DB, PC, PG, MD; 26 weeks	Advanced fluctuations	472	Change from baseline in total daily off-time and adverse event frequency	Rasageline decreased daily off-time and improved the motor fluctuations and PD symptoms in L-DOPA treated patients.
Pfeiffer et al. (2007)	Apomorphine	RD, DB, PC; 3 months	Advanced fluctuations	62	Change in UPPERS motor score	Apomorphine increased UPPERS *vs.* placebo. No significant differences in adverse side effects. Decrease in daily off episodes.
Olanow et al. (2008a, 2009a) ADAGIO study	Rasagiline	DB, DS, MD; 72 weeks	Early untreated	1176	Change in UPPERS (I, II, III, IV)	Early treatment with rasagiline at a dose of 1 mg/day provided benefits (*e.g.*: increase in UPPERS scores), consistent with a possible disease-modifying effect. However, early treatment of rasagiline with 2 mg/day did not. Therefore, rasagiline disease modifying effects must be interpreted with caution.

Key: CO (cross-over); DB (double-blind); DS (delayed start); MC (multicenter); MD (multi-dosage); PC (placebo controlled); PG (Parallel group); RD (randomized); UPPERS (Unified PD rating scale); UPPERS I: evaluates mental cognition, behavior and mood disabilities; UPPERS II: evaluates quality of life/activities of daily life disabilities; UPPERS III: evaluates motor impairment; UPPERS VI: evaluates complications of therapy.

Bergman et al., 1990; Rascol et al., 2011), provided key insights for the "renaissance" of neurosurgical therapies for PD.

Approved by FDA in 2002, DBS consists in the implantation of internal and external electric stimulators (like a pacemaker device) with the aim of delivering continuous high frequency electric stimulation to areas within the brain (Faggiani and Benazzouz, 2016; Schwalb and Hamani, 2008; Smith et al., 2012). In fact, when compared to the first surgical procedures in this area, DBS has overtaken pallidotomy in developed countries, since it presents less significant risks (*e.g.*, hemorrhage, infarction, facial palsy, dysphagia, mortality) and adverse effects (*e.g.*, affective disorders; visual fields, speech and cognitive deficits) than the latter (Pereira and Aziz, 2006; Rascol et al., 2011). DBS of the subthalamic nucleus (STN) and the internal pallidal segment (internal globus pallidus/GPi) is currently the most commonly applied surgical treatment in patients with tremor, dyskinesias, rigidity and motor fluctuations refractory to the presently available medication (Benabid et al., 2009a,b; Pereira and Aziz, 2006; Rascol et al., 2011; Smith et al., 2012). Nevertheless, the ideal target for DBS is still a matter of debate. In fact, clinical trials have related STN DBS to significant cognitive and psychiatric side effects, such as depression, apathy, impulsivity, emotional instability and increased risk of suicide (Anderson et al., 2005; Follett et al., 2010; Moro et al., 2010; Okun, 2013; Schupbach et al., 2005; Soulas et al., 2008; Strutt et al., 2012; Taba et al., 2010). The underlying cause for these events, when reported following DBS surgery either in STN or in the GPi, has not yet been established, but it is thought to involve stimulation of non-motor areas of these targets, along with the limbic structures, as well as pre-surgical psychiatric conditions (Follett et al., 2010; Okun et al., 2009). A summary of the type of surgery, study design, duration and number of patients as well as the primary outcome measure, main results and conclusions from trial studies referenced in this section is provided in Table 2.

3.3. New drugs and surgical targets for PD

Motor complications associated with long-term L-DOPA treatment, as well as the suggestion that some drugs (*e.g.*, selegiline,

Table 2
Summary of key clinical trials conducted using functional neurosurgery for treatment of PD patients' motor symptomatology.

References	Drug(s)	Study design	Patients	Nr. of subjects	Primary outcome measure	Results
Anderson et al. (2005)	Bilateral STN *vs.* GPi DBS	Blinded, RD, PG; 12 months	Prominent bradykinesia and rigidity	25	UPPERS III in off-medication	Stimulation in STN or GPi improves off-medication motor scores and L-DOPA-induced dyskinesia for at least 1 year. There is no clear superiority of STN over GPi. Selection of stimulation site should be influenced by symptom profile.
Schupbach et al. (2005)	Bilateral STN DBS	Unblinded; 5 years	Severe L-DOPA responsive PD	37	UPPERS III, UPPERS II	Improvement in UPPERS III and UPPERS II scores. The significant improvement of motor function was sustained 5 years after neurosurgery.
Soulas et al. (2008)	Bilateral STN DBS	Unblinded; 6 months	Advanced PD	200	Suicidal behavior	Two patients (1%) committed suicide and four patients (2%) attempted suicide after surgery, despite fair to excellent motor improvement. Suicidal behavior is a serious potential hazard of STN DBS, and is commonly associated with depression. Other risk factors like increased impulsiveness may also play a part.
Moro et al. (2010)	Bilateral STN and GPi DBS	DB, CO; 5–6 years	Advanced PD	51	UPPERS III	Effectiveness of both STN and GPi DBS in improving L-DOPA-responsive PD signs, L-DOPA-induced dyskinesias, and ADEL. Adverse effects more frequent in STN DBS group.
Follett et al. (2010)	Bilateral STN *vs.* GPi DBS	Blinded, RD; 24 months	Advanced PD	299	UPPERS III	Similar improvement in motor function after either GPi or STN DBS. Use of DAergic medications decreased more in patients undergoing STN stimulation.
Okun (2013) and Taba et al. (2010)	Unilateral *vs.* Bilateral DBS GPi *vs.* STN	Unblinded, RD; 6 months	Advanced PD	44	UPPERS III, UPPERS IV	Bilateral implantation more suitable for patients with high III-III scores, more symmetric PD, severe gait dysfunction, or dyskinesias. Unilateral DBS suitable for patients with asymmetric UPPERS III scores and moderate gait disturbances.

Key: DBS (Deep brain stimulation); GPi (internal globus pallidus), subthalamic nucleus (STN); CO (cross-over); DB (double-blind); PG (Parallel group); RD (randomized); UPPERS (Unified PD rating scale); UPPERS III: evaluates complications of therapy; UPPERS VI: evaluates complications of therapy; ADEL: activities of daily living;.

rasagiline) could have neuroprotective effect on PD, led to the development of new drugs for symptomatic or neuroprotective therapies. Symptomatic drug therapies for motor features of PD, already being tested in clinical trials, involve for instance the use of DAergic drugs such as controlled-release formulations (IPX 066), continuous duodenal infusions of carbidopa-levodopa (LCIG/Duodopa) and sustained release formulations of L-DOPA (XP 21279). Other strategies have been followed, namely by using drugs targeting non-DAergic neurotransmitter systems, such as adenosine receptor antagonists (*e.g.*, preladenant; tozadenant; caffeine), alpha-2-adrenergic antagonists (*e.g.*, fipamezole), noradrenergic reuptake inhibitors (*e.g.*, methylphenidate), ionotropic (*e.g.*, talampanel) or metabotropic glutamate receptor antagonists (*e.g.*, mavoglurant, dipraglurant), serotonin receptor agonists (*e.g.*, sarizotan, pardoprunox), nicotinic receptor agonists (*e.g.*, nicotine), histamine receptor antagonists (*e.g.*, famotidine), cholinesterase inhibitors (*e.g.*, donepezil, rivastigmine), calcium channel blockers (*e.g.*, isradipine) and endogenous neurotrophic factor inducers (*e.g.*, cogane) [more information on this topic can be found in Hauser (2011), Kalia et al. (2013) and Rodnitzky (2012)]. Some of the above referred drugs (*e.g.*, nicotine, preladenant) are also being studied in clinical trials for the potential neuroprotective part they can play in the scope of PD (source: clinicaltrials.gov; clinical trial identifiers: NCT01560754, NCT01155479) [more information on this topics in Dunkel et al. (2012) and Kalia et al. (2013)]. On the other hand, new drugs targeting oxidative-stress (*e.g.*, deferiprone), mitochondrial dysfunction and excitotoxicity (*e.g.*, creatine) (Rascol et al., 2011; Schapira, 2005) are also currently being tested in clinical trials (NCT01539837, NCT00449865) to determine their possible neuroprotective role in PD [reviewed by Dunkel et al. (2012), Kalia et al. (2013) and Rodnitzky (2012)].

Electrode implantation in patients has also provided insight into the patho-anatomy and pathophysiology of PD. These progresses led to the establishment of possible new targets for DBS such as pedunculo pontine nucleus and caudal zona incerta [reviewed by Sackeim and George (2008)]. These targets generated interest for DBS in PD patients since some small clinical trials reported anti-parkinsonian effects following the stimulation of either pedunculo pontine nucleus (Ferraye et al., 2010; Plaha and Gill, 2005) or zona incerta (Kitagawa et al., 2005; Plaha et al., 2006). Therefore, new clinical trials are planned to study pedunculo pontine nucleus (NCT01485276, NCT02318927) and zona incerta (NCT01945567) as potential DBS targets for PD therapy.

4. Molecular therapies

As discussed before, the long-term use of L-DOPA has been associated with undesirable side effects, such as motor fluctuations and dyskinesias (Schapira, 2005; Smith et al., 2012; Teixeira et al., 2013). These limitations, together with significant advances made in the study of the pathobiology and patho-anatomy of PD, led to the emergence of new pharmacologic agents and gene engineering approaches for the long-term outcome of PD patients.

4.1. Drug therapy

Nowadays, new candidate drugs, still in preclinical studies, focus mainly on neuroprotective agents, as well as on alternative non-DAergic therapies, for PD treatment. Based on recent animal model studies, metabotropic glutamate receptor agonists have raised special attention as potential neuroprotective targets in PD (Marino and Conn, 2006). Among the type of agonists mentioned, subtype 4 of group III (mGluR4) is mainly localized in presynaptic terminals and mediates inhibitory effects on basal ganglia circuitry, namely on glutamatergic synapses in the striatum and GABAergic synapses in the globus pallidus (Nicoletti et al., 2011; Smith et al., 2012). DA depletion in PD has been associated with basal ganglia circuitry hyperactivation. Electrophysiological studies have demonstrated that activation of mGluR4 significantly reduces excitatory synaptic transmission within the basal ganglia (Bennouar et al., 2013; Cartmell and Schoepp, 2000). For these reasons, interest has been raised about the use of mGluR4 agonists, and more recently about enhancers of the mGluR4 agonist effect (positive allosteric modulators), as potential anti-parkinsonian therapies. Indeed, several studies have shown that drugs which activate mGluR4, such as orthosteric agonists (*e.g.*, (2S)-2-amino-

4-[hydroxy[hydroxy(4-hydroxy-3-methoxy-5-nitro-phenyl)methyl]phosphoryl]butanoic acid/LSP1-2111) and positive allosteric modulators [(*e.g.*, *N*-phenyl-7-(hydroxylimino)cyclopropa[*b*]chromen-1a-carboxamide (PHCCC); (+/−)-cis-2-(3,5-dichlorphenylcarbamoyl)cyclohexanecarboxylic acid/VU0155041, and 5-Methyl-N-(4-methylpyrimidin-2-yl)-4-(1H-pyrazol-4-yl)thiazol-2amine/ADX88178)], crossed the brain–blood-barrier and alleviated PD motor symptoms (*e.g.*, akinesia and drug-induced dyskinesias) in animal models (Betts et al., 2012; Beurrier et al., 2009; Niswender et al., 2008). For instance, allosteric modulators like PHCCC have shown to reduce loss of nigrostriatal dopaminergic neurons in a mice model of PD, following its injection in the external globus pallidus (Battaglia et al., 2006). Similar results regarding neuroprotection of DAergic neurons and motor benefits were reported by Betts et al. after injection of VU0155041 in the SNpc of a rat model of PD (Betts et al., 2012). These results suggest that mGluR4 allosteric modulators may play a dual role, by relieving PD motor symptoms and providing neuroprotection of the nigrostriatal pathway. Indeed, recently developed positive allosteric modulators, like ADX88178, demonstrated to improve efficacy in a rodent PD model when combined with L-DOPA and adenosine receptor antagonists (Amalric et al., 2013; Celanire and Campo, 2012). Taken together, current experimental data on mGluR4 agonist effects on general PD motor symptoms and neuroprotection of the nigrostriatal pathway are promising. Importantly, non-motor side effects should also be assessed in future animal studies. This is a matter to be taken in account, since it was reported in human studies following administration of several ionotropic glutamate receptor antagonists, aimed at blocking increased glutamatergic transmission in the basal ganglia circuitry (Maranis et al., 2012).

In addition to mGluR4 agonists, CEP-1347 has also been proposed as a possible disease modifying agent for the treatment of PD (Parkinson Study, 2004). CEP-1347 has been described as an anti-apoptotic drug able to inhibit the mixed lineage kinases, which are activators of apoptotic pathways implicated in the pathogenesis of PD (Eggert et al., 2010). From the application point of view, this drug was found to enhance neuronal survival in a variety of pre-clinical models and also to be safe and well tolerated in PD (Harikrishna Reddy et al., 2014). Indeed, CEP-1347 did not alter the pharmacokinetics of L-DOPA in PD patients, when both you administered in combination (Parkinson Study, 2004). Despite these promising observations, application of CEP-1347 remains controversial. In 2007, The Parkinson Study Group PRECEPT Investigators (Parkinson Study Group, 2007) reported that, contrarily to the effects showed in animal models (CEP-1347 acting as a favorable disease-modifying agent), in humans CEP-1347 demonstrated to be an ineffective treatment in early PD. Similar results were also found in a phase II clinical trial conducted with approximately 800 participants, which was terminated because CEP-1347 did not cause any significant decline in PD progression (Group, 2005b).

GM1 ganglioside has also been described, like CEP-1347, as a potential disease modifying therapy for PD (Pope-Coleman et al., 2000; Schneider et al., 1998). Being a normal constituent of nerve cell membranes, it is described as a modulator of several cell surface and receptor activities. It also plays a role in neuronal differentiation, protein phosphorylation and synaptic function (Pope-Coleman et al., 2000; Schneider et al., 1995). GM1 has demonstrated to be effective in ameliorating neurochemical and behavioral alterations both in murine and non-human primate PD models (Herrero et al., 1993; Schneider et al., 1995). In 1998, Schneider and colleagues (Schneider et al., 1998), in a randomized double blind placebo trial, showed that the administration of GM1 led to the improvement of UPDRS motor scores and performance in motor tasks from PD patients, when compared to the baseline performance. More recently, in a five-year open study, Schneider and colleagues (Schneider et al., 2010) demonstrated that the long-term application of GM1 in PD patients is safe and may provide some clinical benefits. Nonetheless, these authors also claim the need for future studies to completely address if GM1 may be a symptomatic or disease modifying compound for the treatment of PD (Schneider et al., 2013, 2010). Following this, in a recent pilot imaging study Schneider and colleagues (Schneider et al., 2015) provided insights about the application of GM1 improving dopamine neurotransmission in patients, which might indicate GM1 as potential disease modifying agent for PD. Although the precise mechanism for this has not been described, studies have claimed that GM1 action in PD patients is multi-factorial (Schneider et al., 2013). Indeed, in a recent work performed by Hadaczek and colleagues (Hadaczek et al., 2015) it was suggested a potential neuroprotective role of GM1, through GDNF signaling, an important growth factor for the maintenance of DAergic viability.

Coenzyme Q10 (CoQ10), a pivotal enzyme in the oxidative phosphorylation process in mitochondria, has also been presented as a potential disease modifying agent for the treatment of PD (Seet et al., 2014). However, the clinical evidence for CoQ10 in PD is still conflicting. For instance, Muller and colleagues (Muller et al., 2003) showed significant symptomatic improvements following CoQ10 administration during four weeks, while similarly, Shults and colleagues (Shults et al., 2002) observed long-term benefits of CoQ10 up to 16 months. On the other hand, Storch and colleagues (Storch et al., 2007), using the same dose that the previous study reported (1200 mg/day), did not observe benefits in mid-stage PD after 3 months of treatment. More recently, in a phase III randomized clinical trial (Parkinson Study Group et al., 2014), it was demonstrated that CoQ10 was safe and well tolerated in PD patients, but did not present evidence of clinical benefits. Thus, additional trials are still needed to really confirm the potential role of CoQ10 in slowing or modifying the progressive deterioration function in PD.

Finally, *N-acetyl-cysteine* (NAC) has been described as a thiol antioxidant and a prodrug which can systematically deliver cysteine to the brain (Martinez Banaclocha, 2000; Tarazi et al., 2014). Studies in animal models have reported that NAC administration leads to the reduction of oxidative damage, by increasing mitochondrial complex I activities and preventing ROS accumulation, leading this way to the protection of dopamine-induced cell death (Clark et al., 2010; Martinez-Banaclocha, 2012). In a recent clinical trial, Holmay and colleagues (Holmay et al., 2013) demonstrated that, after intravenous injection of NAC, there was a boost in antioxidant glutathione levels on the brain and blood of PD patients. Such increases may compensate the hypothesized deficiency and lower glutathione activity in PD (Jenner, 2003, 2007). More recently, Monti and colleagues (Monti et al., 2016) revealed that NAC may support DAergic viability and functionality through dopamine modulation. Nevertheless, more studies are still needed to investigate the potential benefits of NAC in improving PD symptomatology or slowing its progression, whether as a monotherapy, whether or in combination with L-DOPA.

4.2. Gene therapy

Gene therapy in PD makes use of viral vectors to carry out gene transfer for targeted protein expression in specific brain areas. In the last decade, the use of gene therapy to relieve PD motor symptoms has reached clinical trials essentially through three approaches: (1) delivery of glutamic acid decarboxylase (GAD) enzyme in the STN; (2) delivery of synthetic enzymes to increase striatal DA levels, and (3) local infusion of neurotrophic factors to protect and restore nigral DAergic neurons (Cummins and Barker, 2012; Rodnitzky, 2012; Smith et al., 2012).

The rationale behind the first approach is to deliver GAD, the rate-limiting enzyme for GABA synthesis, into the glutamatergic neurons of the STN, using an adeno-associated virus (AAV) vector. This gene therapy approach aims at modulating STN activity, by modifying the phenotype of the STN neurons from predominantly excitatory (glutamatergic) to predominantly inhibitory (GABAergic). With this it is expected that the normal function in striatopallidal circuitry can be restored (Coune et al., 2012; Smith et al., 2012). Based on preclinical data provided by animal models of PD (Emborg et al., 2007; Lee et al., 2005; Luo et al., 2002), as well as the reported improvement of motor scores in a phase I open-label study involving 12 moderately advanced PD patients (Kaplitt et al., 2007), a phase II, double-blind, randomized, sham-controlled trial enrolling 45 advanced PD patients, was conducted (LeWitt et al., 2011). Results revealed a modest but significant improvement in UPDRS motor scores of patients bilaterally infused with STN AAV-GAD. The most common adverse effects reported were nausea, headache and depression. A five year follow up of adeno-associated virus serotype 2 (AAV2) vector encoding glutamic acid decarboxylase in the subthalamic nucleus (STN AAV2-GAD) is currently on-going to evaluate long-term effects of AAV-GAD gene transfer and its long-term safety (NCT01301573).

The second gene therapy approach consists of the transfection of dopamine-synthesizing enzymes, to induce DA synthesis in the striatum in order to alleviate PD motor symptoms. So far, two different enzyme replacement therapies have been tested in clinical trials. In the first open label phase I/II trial conducted in 2007, a lentiviral vector containing the genes encoding for the enzymes required for DA biosynthesis (tyrosine hydroxylase/TH, guanosine 5′-triphosphate/GTP cyclohydrolase 1 and aromatic amino acid decarboxylase/AADC), under the name of ProSavin, was injected into the striatum to evaluate the safety, efficacy and dosage in 15 mid-to-late stage PD patients, for a period of 6 months (NCT00627588). The Oxford biomedical company recently reported good tolerance of ProSavin. Moreover, motor improvements were observed 6 months after the test had begun, as assessed by UPDRS motor scores. A multicenter, open label study for a ten-year follow-up of patients who were treated with ProSavin to evaluate its long-term safety, tolerability and efficacy for PD treatment is currently ongoing (NCT01856439). The second enzyme replacement therapy, tested in two phase I clinical trials, consisted in bilateral intra-putaminal or intrastriatal delivery of an AAV encoding human AADC gene to induce local conversion of peripheral administered L-DOPA into DA (Christine et al., 2009). Although preclinical studies in a non-primate model of PD had previously showed that AAV-AADC could induce stable long-term expression of the vector, restore L-DOPA levels, improve motor deficits and reduce L-DOPA side effects in subjects (Bankiewicz et al., 2006, 2000), both phase I clinical trials reported only modest improvements in UPDRS scores of advanced PD patients. Moreover, in one of the clinical trials (Christine et al., 2009), some patients suffered from aggravated dyskinesias, most likely due to non-regulated striatal neurons release of DA. A non-randomized open label trial to evaluate safety and efficacy of AAV2-human AADC injected through magnetic resonance imaging guidance is currently being planned (NCT01973543). However, future trials must be designed with caution to avoid excessive production of dopamine in the striatum, since GABAergic striatal neurons do not possess vesicular storage capability. This lack of vesicular structures can result in accumulation of extracellular or cytosolic DA, which in turn may lead to oxidative-stress (Chen et al., 2008), dyskinesias (Bankiewicz et al., 2006, 2000) and even to degeneration of striatal neurons (Chen et al., 2008; Cyr et al., 2003).

The third gene therapy approach relies on the use of growth factors, such as GDNF, to mediate growth, survival and protection of DAergic neurons within the midbrain (Sherer et al., 2006). Due to its tropism for the nigral DAergic neurons, GDNF was amongst the first molecules to be studied (Ai et al., 2003; Grondin et al., 2003, 2002). However, two double-blind trials reported no improvement of Parkinson motor symptoms following infusion of GDNF, either in the lateral ventricles or in the putamen, with many patients suffering from diverse side effects (Lang et al., 2006; Nutt et al., 2003). Based on these results, the attention has shifted toward neurturin (NTN), a member of the GDNF ligands family that, similarly to GDNF, has shown to promote survival and growth of midbrain DAergic neurons (Kotzbauer et al., 1996). Recently, the efficacy and safety of an adenovirus vector encoding for human NTN (AAV2-NTN), under the name CERE-120, has been evaluated in two clinical trials. A phase I clinical trial enrolling 12 PD patients demonstrated good tolerance to AAV2-NTN and an improvement in "off" medication symptoms (Marks et al., 2008). This led to a phase II multicenter, randomized, double-blind, sham-controlled trial involving intraputaminal injection of AAV2-NTN in 58 patients with moderate to severe PD (Marks et al., 2010). However, in this new study results revealed no improvements in UPDRS motor "off" score. Also, contrarily to the results observed in pre-clinical non-human primate studies (Herzog et al., 2008, 2007; Kordower et al., 2006), post-mortem brain analysis of AAV2-NTN treated patients revealed the expression of NTN mainly in the striatum with minimal presence in the SNpc (Marks et al., 2010). This result has been associated with the lack of retrograde transportation of NTN to the SNpc and the extensive loss of DAergic neurons in advanced PD patients (Bartus et al., 2011). Consequently, a new phase I/II trial, in which AAV2-NTN is injected into the SN and the putamen, is presently being conducted in earlier stage patients to evaluate safety and potential beneficial effects of AAV2-NTN over longer periods of time (NCT00985517). So far, phase I has been completed in 6 subjects with no reported complications.

In spite of the encouraging preclinical data, clinical trials based on therapeutic transgenes delivery to basal ganglia neuronal populations failed to confirm the beneficial motor effects observed in animal studies (with the exception of the first approach). This way, genetic approaches still have to prove its long-term efficacy and long-term safety as an alternative therapy for the existing symptomatic treatments. Nevertheless, recent insights on the genetic causes of PD, as well as the development of innovative gene delivery systems, may shed some light on this topic in the years to come.

5. Cell-based therapies

The hypothesis that therapies using cells could be a good strategy to replace DAergic neurons lost along the course of PD, led to the emergence of cell-based approaches to meet the clinical challenge of restoring degenerated DAergic neural circuitries and provide long-lasting relief of patients symptoms. In this section, the characterization, advantages and disadvantages of each of these cell-based therapies will be further explored.

A summary of the advantages and disadvantages of different stem cell types for application in PD is provided in Table 3.

5.1. Fetal ventral mesencephalic tissue

Fetal ventral mesencephalic (FVM) tissue is derived from the fetuses' midbrain (Shamekh et al., 2008). The rationale for its transplantation relied on the hypothesis that healthy DAergic neurons are able to reinnervate the striatum and restore physiological DA transmission in the brain. In the late 1970s, several grafting studies were conducted using FVM tissue transplanted either into the lateral ventricle adjacent to the caudate (Perlow et al., 1979) or directly into the striatal parenchyma (Björklund et al., 1980), on 6-hydroxydopamine (6-OHDA) models

Table 3
Advantages and disadvantages of different stem cell types for application in PD.

Cell type	Advantages	Disadvantages	References
ES cells	• High proliferative pluripotent cell source • Retain pluripotency for long periods of *in vitro* expansion • Can be differentiated into DAergic neurons • Derived DAergic neurons were shown to survive, integrate and reinnervate the striatum of the host, thus improving functional recovery of PD symptoms	• Risk of tumor formation related with phenotypical instability of grafts • Ethical concerns • No data in non-human primate models of PD	Bj&rklund et al. (2002), Brederlau et al. (2006), Kim et al. (2002), Politis and Lindvall (2012a,b), Roy et al. (2006) and Salgado et al. (2006)
Fetal NSCs	• Expandable multipotent cell source • Can be differentiated into DAergic neurons • Midbrain NSCs-derived DAergic neurons were shown to survive, differentiate, migrate and induce functional recovery in PD animals	• Limited differentiation *in vivo* • Technical problems obtaining homogenous populations of DAergic neurons • Safety issues related with the use of retroviral vectors for differentiating adult NSCs into DAergic neurons • Ethical concerns	Carvey et al. (2001), Parish et al. (2008), Politis and Lindvall (2012b), Sanchez-Pernaute et al. (2001), Sawamoto et al. (2001) and Schwarz et al. (2006)
iPS cells	• Expandable cell source • Reprogrammable from somatic cells • Possibility of generating patient-specific donor cells for autologous transplantation • Reduced probability of immune rejection • No ethical concerns • Derived DAergic neurons have shown to survive and induce functional benefits in PD animals	• Differentiation pattern variability *in vivo* • Risk for teratoma formation • Autologous transplantation: risk of susceptibility for the original pathology, related with possible genetic mutations present in patients fibroblasts • No data in non-human primate models of PD	Hargus et al. (2010), Politis and Lindvall (2012b), Swistowski et al. (2010) and Wernig et al. (2008)
MSCs	• Easy to isolate, expandable in culture and great proliferative potential with minimal senescence through multiple passages • Isolated from different tissue sources • Obtained with minimal invasive procedures • Safe source for autologous transplantation • Possess immunosuppressive function • Secrete a vast panel of growth factors and cytokines • Less prone for tumor formation • Not hindered by ethical concerns • Undifferentiated MSCs have shown not only to survive and migrate toward the injured site and to promote neuroregeneration in PD animals, but also to ameliorate animals' motor deficits through the secretion of bioactive molecules	• Full differentiation of MSCs-derived DAergic neurons remains to be proven • No data on undifferentiated MSCs transplantation in non-human primate models of PD • Transplantation of BMSCs provided only modest clinical improvement in humans	Blandini et al. (2010), Bouchez et al. (2008), Cova et al. (2010), Hayashi et al. (2013), Kim et al. (2009), Kishk and Abokrysha (2011), Levy et al. (2008), McCoy et al. (2008), Offen et al. (2007), Park et al. (2012), Sadan et al. (2009), Salgado et al. (2006), Shetty et al. (2009), Teixeira et al. (2013), Venkataramana et al. (2010), Wang et al. (2010), Wang et al. (2013), Weiss et al. (2006), and Zhou et al. (2013a)

of PD. These studies showed that transplantation of DAergic tissue or cells induced the recovery of motor functions, which was associated with graft-derived reinnervation of most of the caudate-putamen. Subsequent studies consistently demonstrated that intrastriatal transplantation of rat fetal SN tissue could reinnervate rat striatum, secrete DA and induce substantial, or even complete, reversion of motor deficits (Björklund and Kordower, 2013; Dunnett et al., 1983, 1988; Koller, 2003). The extent of the animals' motor recovery largely depended on the extent of nigrostriatal reinnervation and DA restoration following SN transplants. Thus, the observation that animal's behavioral recovery could only be achieved with striatal intra-parenchyma grafting led to the abandonment of intraventricular transplantation (Björklund and Kordower, 2013). In the late 1980s, the first human open trials were performed and revealed promising results on the long-term survival of DAergic neurons as well as DA synthesis, following human FVM tissue transplantation (Hagell et al., 1999; Koller, 2003; Kordower et al., 1996; Lindvall et al., 1990; Wenning et al., 1997; Widner et al., 1992). Motivated by these encouraging results, two National Institute of Health funded double-blind placebo-controlled trials were conducted in advanced PD patients (Freed et al., 2001; Olanow et al., 2003). However, both studies failed to meet their primary outcome concerning long-term survival of DAergic neurons and some patients developed severe graft-induced dyskinetic side effects postoperatively. In addition, Lewy bodies degeneration was observed in the patients that have been examined post-mortem, ten to sixteen years after human FVM tissue transplantation (Kordower et al., 2008; Li et al., 2008; Rascol et al., 2011). Moreover, methodological and ethics related issues associated with human FVM tissue harvesting have also hindered its use in PD therapeutics (Azari et al., 2010; Teixeira et al., 2013). Nevertheless, the reported improvement in striatal DAergic neurons and functional outcome in some patients with PD resulted in a currently ongoing phase I European clinical trial (TRANSEURO – NCT01898390). For this trial, an optimized tissue preparation protocol to reduce the graft-induced dyskinesias has been applied.

5.2. Embryonic stem cells

Embryonic stem (ES) cells are derived from the inner cell mass of the blastocyst. They are considered to be pluripotent cells due to their capability to differentiate into the three germ layers (endoderm, mesoderm and ectoderm) of the embryo (Salgado et al., 2006). ES cells are highly proliferative cells, able to maintain their pluripotency for long periods of *in vitro* expansion (Politis and Lindvall, 2012a). The possibility of establishing large-scale production of ES cells and to differentiate them into DAergic neurons, led to the possibility of these cells being considered as a tool for generating new cell-based PD therapeutic protocols (Cho et al., 2008; Park et al., 2004; Perrier et al., 2004). Numerous animal experiments using either rodent or human ES cells-derived dopaminergic neurons showed that these cells could induce functional recovery in animal models of PD (Ben-Hur et al., 2004; Björklund et al., 2002; Brederlau et al., 2006; Kim et al., 2002; Yang et al., 2008b). Indeed, Björklund et al. and Kim et al., demonstrated that striatal grafted ES cells-derived DAergic neurons were able to survive, integrate and reinnervate the striatum, and this way

improve animals' behavior (Björklund et al., 2002; Kim et al., 2002). Björklund at al. (2002) also observed that the degree of striatal reinnervation was correlated with animals' behavior improvement, an observation that has again been reported by Yang and colleagues (Yang et al., 2008b). However, despite the consistent description of animals' motor improvement following ES cells-derived DAergic neurons grafting, phenotypic instability of the grafts and consequent tumor formation in rats has also been reported (Brederlau et al., 2006; Roy et al., 2006). Therefore, issues related with safety and ES cells inappropriate differentiation into midbrain neurons have severely hampered its clinical application. Kriks et al. (2011) has recently readdressed these concerns, which might bring back ES cells into the clinical arena. Still, human ES cells use in clinics is surrounded by controversy related with possible immune rejection of the grafts as well as with safety and ethical issues.

5.3. Neural stem cells

Neural stem/precursor cells (NSCs) are multipotent cells, capable of differentiating into the main phenotypes of the central nervous system, namely neurons, astrocytes and oligodendrocytes (Yi et al., 2013). NSCs can be isolated from developing or adult central nervous system tissue (Bennett et al., 2009; Meyer et al., 2010) and cultured *in vitro* as free-floating spheres (neurospheres) in the presence of endothelium growth factor and/or basic fibroblast growth factor (Bonnamain et al., 2012). Their intrinsic properties, and the prospect of using them for replacement of lost DAergic neurons and reconstitution of the DAergic transmission, raised great interest in the use of NSCs as a source for cell replacement therapy in PD.

The first studies using undifferentiated embryonic or fetal NSCs, isolated from cortical and midbrain areas of rodent developing brain, not only reported poor survival and differentiation of striatal grafted cells into DAergic neurons in animal models of PD, but also only mild amelioration of lesion induction deficits (Svendsen et al., 1997; Svendsen et al., 1996). In addition, these and other studies have consistently reported that only NSCs isolated from the midbrain could differentiate into DAergic neurons (Meyer et al., 2010; Sanchez-Pernaute et al., 2001; Storch et al., 2001, 2004). Since then most transplantation studies use either rodent (Carvey et al., 2001; Sawamoto et al., 2001; Schwarz et al., 2006) or human fetal NSCs (Sanchez-Pernaute et al., 2001) differentiated into DAergic neurons *in vitro* prior to transplantation. These studies showed that striatal transplantation of fetal NSCs-derived DAergic neurons resulted in histological, biochemical and functional recovery in animal models of PD. Moreover, one of these studies reported NSCs to have a milder immune rejection and lower risk of tumor formation than ES cells (Schwarz et al., 2006). However, despite these encouraging results, a low percentage of the transplanted cells survived and/or adopted the DAergic phenotype *in vivo* after both short- and long-term *in vitro* expansion of NSCs (Carvey et al., 2001; Sawamoto et al., 2001; Schwarz et al., 2006). These results, together with the mild-benefits observed in the functional recovery of PD animals reported in earlier studies (Svendsen et al., 1997, 1996), have been associated with NSCs dependence on developmental signals (*e.g.*, fibroblast growth factor 8 and Sonic hedgehog) and transcription factors (*e.g.*, nuclear receptor realated-1 protein) (Storch et al., 2004) implicated in DAergic neurons development (Perrone-Capano and Di Porzio, 2000; Storch et al., 2004). Parish et al. proposed that an alternative method to address this issue was through the culture of genetically engineered NSCs cells, together with developmental signals necessary for inducing DAergic neurons differentiation *in vivo* (Parish et al., 2008). Using this alternative method, the generation of higher yields of functional DAergic neurons *in vitro*, along with an enhancement in TH-positive cells engraftment and in striatal reinnervation *in vivo*, was obtained. These improvements were followed by complete behavior recovery of parkinsonian rodents, without tumor formation (Parish et al., 2008). Nevertheless, long-term follow up of the animals should be provided in order to ensure safety of these engineered cells. Despite the progresses achieved with mesencephalic derived NSCs, the long-term survival and phenotype stability of grafted DAergic neurons in animal models of PD still remains to be demonstrated. Therefore, standardization of protocols ensuring the control of NSCs differentiation into homogeneous populations of DAergic neurons should be established and their transplantation effects in parkinsonian models must be further explored.

5.4. Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) recently emerged in the field of regenerative medicine, following the pioneer studies provided by Takahashi and colleagues (Takahashi et al., 2007; Takahashi and Yamanaka, 2006) in which the authors showed that fibroblasts derived from mice or humans could be re-programmed into pluripotent stem cells. These studies demonstrated that iPS cells presented morphological and phenotypical properties similar to ES cells, particularly pluripotency and generation of viable chimeras (Brundin et al., 2010; Takahashi et al., 2007; Takahashi and Yamanaka, 2006). Subsequent studies showed that iPS cells not only exhibited genomic stability and transcription profiles similar to ES cells, but were also able to use the same transcriptional network and developmental patterning cues as them to differentiate into DAergic neurons (Brundin et al., 2010; Gibson et al., 2012; Swistowski et al., 2010; Wernig et al., 2008). In reality, these cells can hold advantages over ES cells, such as the possibility of generating patient specific donor cells for autologous transplantation and this way avoid both immune rejection and ethical concerns related with the use of ES cells (Wernig et al., 2008).

Studies on transplantation of iPS cells into the striatum of PD animals, either obtained from mice or PD patients somatic cells, provided proof-of-principle for their ability to survive and induce functional benefits in PD animals (Hargus et al., 2010; Swistowski et al., 2010; Wernig et al., 2008). However, these studies also reported variability in the differentiation pattern of iPS cells into DAergic neurons *in vivo*. It has also been observed that tumor (teratoma) formation can occur if iPS cells grafts are not fully differentiated prior to transplantation (Wernig et al., 2008). Moreover, DAergic neurons differentiated from patient-derived iPSCs exhibit a remarkable reduction in the number of neurites and an increased accumulation of autophagic vacuoles when compared to DAergic neurons derived from iPSCs of healthy controls (Sanchez-Danes et al., 2012).

5.5. Induced neural cells

In an attempt to address the complications related with incomplete and unsynchronized differentiation of iPS cells observed *in vivo* (Hargus et al., 2010; Wernig et al., 2008), an interesting alternative approach, consisting in directly reprograming one somatic cell type into another, was proposed some years ago by Melton and colleagues (Zhou et al., 2008). Vierbuchen et al. have also reprogrammed fibroblasts into functional neurons *in vitro* using a similar combinatorial strategy of three neural-specific transcription factors (Brundin et al., 2010; Vierbuchen et al., 2010). The resulting cells were named induced neural cells (iN cells). These cells have shown the capability to generate DAergic neurons *in vitro*, while avoiding the reversion to a pluripotent stage, therefore diminishing the risk for tumor formation. However, the

ability of these iN cells-derived DAergic neurons to induce benefits on PD animals' phenotype remains to be demonstrated (Caiazzo et al., 2011; Gibson et al., 2012; Pfisterer et al., 2011).

5.6. Mesenchymal stem cells

Mesenchymal stem/stromal cells (MSCs) were initially reported by Friedenstein and colleagues, that defined cells isolated from bone marrow as plastic-adherent fibroblast colony-forming units with clonogenic capacity (Friedenstein et al., 1974). These cells were named in 1991 as marrow "stromal cells" by Eaves et al., based on their possible use as a feeder layer for hematopoietic stem cells (Eaves et al., 1991). In that same year, these cells also became known as mesenchymal stem cells on the basis of the report on their clonogenicity and ability to undergo multilineage differentiation, published by Caplan and colleagues (Caplan, 1991). Currently MSCs are defined, according with the International Society for Cellular Therapy criteria, as multipotent cells, capable of self-renewal and of differentiating into adipocytes, osteoblasts and chondroblasts (Emsley et al., 2005). Additionally, MSCs have also been characterized by their ability to adhere to tissue culture plastic and to display the presence of cells surface markers (CD105, CD73, CD90), as well as the lack of hematopoietic cell surface markers (CD45, CD34, CD14 or CD11b, CD79a or CD19 and Human Leukocyte Antigen DR) (Dominici et al., 2006). So far, MSCs have been isolated from bone marrow (BMSCs), adipose tissue (ASCs), dental pulp, placenta, amniotic fluid, umbilical cord blood, umbilical cord Wharton's jelly (WJ-MSCs/HUCPVCs), liver, lung and spleen (Teixeira et al., 2013). They have been reported to be isolated with minimal invasive procedures; easily cultured and expanded *in vitro* for several passages; used for autologous transplantation in virtue of their hypo-immunogenicity (probably related with their surface expression of major histocompatibility complex antigens); have less probability of being tumorigenic and, as adult cells, not hindered by ethical concerns (Kishk and Abokrysha, 2011; Salgado et al., 2006; Seo and Cho, 2012; Teixeira et al., 2013). These features have made MSCs attractive tools for tackling central nervous system neurodegenerative diseases. Indeed, a considerable body of evidence has revealed the potential of such cells to promote protection and/or recovery of DAergic neurons, against neurotoxin-induced nigrostriatal degeneration, following intrastriatal (Blandini et al., 2010; Bouchez et al., 2008; Cova et al., 2010; Khoo et al., 2011; McCoy et al., 2008; Sadan et al., 2009; Weiss et al., 2006) intranigral (Mathieu et al., 2012; Somoza et al., 2010), intrathecal (Salama et al., 2012) intravenous (Chao et al., 2009; Wang et al., 2010) and intranasal (Danielyan et al., 2011) delivery of BMSCs, ASCs or WJ-MSCs in rodent or non-human primate models of PD. The mechanisms underlying *in vivo* functional recovery following MSCs transplantation are, however, a matter of intense debate.

Several groups have focused on the application of MSCs as replacers of injured DAergic neurons, using neuronal-induced MSCs – prior to transplantation – in PD animal models (Baer and Geiger, 2012; Hermann et al., 2004; Jiang et al., 2002; Mitchell et al., 2003; Munoz-Elias et al., 2004; Phinney and Prockop, 2007). Indeed, several authors have reported that BMSCs-, ASCs- and WJ-MSCs-derived DAergic neurons transplantation into the striatum, of both rodent and primate models of PD, survived for long periods and increased the levels of DAergic markers. Motor improvement was also described (Hayashi et al., 2013; Levy et al., 2008; Offen et al., 2007; Shetty et al., 2009; Wang et al., 2013; Zhou et al., 2013a). In addition, two of these studies have reported detectable levels of DA in culture medium following *in vitro* BMSCs differentiation into DAergic phenotype or DA release after depolarization by potassium stimulation (Hayashi et al., 2013; Shetty et al., 2009). Similar outcomes were also described after intranigral transplantation of undifferentiated WJ-MSCs and WJ-derived DAergic neurons in a 6-OHDA rodent model of PD (Shetty et al., 2013). In this study, the authors further compared the effect of either naïve or differentiated BMSCs and WJ-MSCs in parkinsonian animals. Results revealed that, both naïve and differentiated WJ-MSCs were able to significantly improve the motor behavior, although this effect was more striking in differentiated WJ-MSCs transplanted animals. In contrast, Bouchez et al. reported similar beneficial effects on animals' behavioral recovery after intrastriatal transplantation of either BMSCs cultured in standard conditions or in neuronal differentiation medium (Bouchez et al., 2008). On the other hand, McCoy et al. showed that ASCs were able to protect DAergic neurons and ameliorate animals' functional deficits against neurotoxin-induced neurodegeneration, without the need of DAergic differentiation (McCoy et al., 2008). Comparable to what Bouchez et al. and McCoy et al. found, other researchers have reported no *in vivo* differentiation of *in vitro* neural-induced MSCs (Chao et al., 2009; Khoo et al., 2011), after intrastriatal or intravenous transplantation in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-OHDA rodent models of PD. Also, robust data failed to provide robust evidence regarding MSCs differentiation into full functional neurons (Liu et al., 2012; Thomas et al., 2011; Trzaska et al., 2007). Therefore, it seems unlikely that MSCs differentiation into neuronal lineages is the major contributor for MSCs-induced recovery in PD.

In recent years, MSCs regenerative effects have been related to their secretome, that is, to the panel of bioactive soluble factors and vesicles with neuroregulatory properties released by these cells to the extracellular environment (Teixeira et al., 2013). Different tissue derived MSCs not only seem to sense local environment, but have also shown to respond to signals that are up-regulated under injury conditions by migrating to the damage site. Once there, they promote cell regeneration and limit the extent of tissue damage through the secretion of soluble growth factors (GFs), anti-inflammatory cytokines and microvesicles/exosomes (Caplan and Dennis, 2006; Ding et al., 2007; Li et al., 2002; Meirelles Lda et al., 2009; Neuhuber et al., 2005; Yang et al., 2008a). The effect of these soluble factors can be generally classified into neuroprotective/anti-apoptotic, neurogenic, angiogenic and synaptogenic. Such effects are commonly mediated by the secretion of the following factors by MSCs (Chen et al., 2000, 2001a,b; Ding et al., 2007; Hu et al., 2010; Li et al., 2002; Lin et al., 2011; Lopatina et al., 2011; Neuhuber et al., 2005; Wakabayashi et al., 2010; Wei et al., 2009; Wright et al., 2007): brain-derived neurotrophic factor (BDNF), GDNF, nerve growth factor, hepatocyte growth factor, vascular endothelial growth factor, vascular endothelial growth factor receptor 3, angiopoietin 1, insulin-like growth factor 1, insulin-like growth factor 2, endothelium growth factor, basic fibroblast growth factor, fibroblast growth factor 20, granulocyte colony-stimulating factor, platelet-derived growth factor AA, chemokine ligand 16, neutrophil-activating-protein-2 and neurotrophin-3 growth factors, as well as interleukin-6, interleukin-10, transforming growth factor beta 1, stem cell factor, stromal cell-derived factor 1 and monocyte chemotactic protein 1 cytokines.

In the context of PD, several studies have also demonstrated that BMSCs secretome has a protective and/or regenerative character on DAergic neurons in *in vitro* and *in vivo* models of PD (Blandini et al., 2010; Cova et al., 2010; Danielyan et al., 2011; Kim et al., 2009; McCoy et al., 2008; Park et al., 2012; Sadan et al., 2009; Shintani et al., 2007; Wang et al., 2010; Weiss et al., 2006). For instance, Shintani and coworkers demonstrated that BMSCs conditioned media was able to promote survival of TH-positive DAergic neurons in rat primary cultures of ventral mesencephalic cells (Shintani et al., 2007). Moreover, intrastriatal transplantation of fetal mesenchephalic cells, pre-treated with human BMSCs conditioned media, induced survival of DAergic grafted cells and

promoted functional recovery in a 6-OHDA rat model of PD (Shintani et al., 2007). The observed protection of DAergic neurons was attributed to BMSCs secretion of BDNF, GDNF and basic fibroblast growth factor, all of which had previously shown to stimulate survival of DAergic neurons (Shintani et al., 2007; Teixeira et al., 2013). Similarly, Sadan et al. showed not only that human BMSCs cultured in the presence of growth factors significantly increased the viability of the SH-SY5Y neuroblastoma cell line exposed to 6-OHDA, but also that BMSCs transplanted into the striatum of a 6-OHDA rat model of PD migrated to the lesion site, increased the number of TH-positive cells and the DA levels (Sadan et al., 2009). These neuroprotective and neuro-regenerative effects were accompanied by a reversion of behavioral impairments and were correlated with BMSCs secretion of significant amounts of BDNF and GDNF. Likewise, this expression pattern is in accordance with data published by Blandini and colleagues using the same animal model (Blandini et al., 2010). On the other hand, Wang and colleagues associated rat-derived BMSCs expression of stromal cell-derived factor 1α with DAergic neurons protection against 6-OHDA neurotoxin, both *in vitro* and *in vivo*, through anti-apoptotic based mechanisms (Wang et al., 2010). Moreover, Cova et al. demonstrated that human BMSCs transplanted into the striatum of a 6-OHDA rodent model of PD were able to survive and interact with the lesion site surroundings, thus enhancing survival of DAergic terminals and neurogenesis in the SVZ in a sustained manner (Cova et al., 2010). Importantly, BMSCs *in vitro* secretion of neurogenic (endothelium growth factor, neurotrophin-3, BDNF), neurodevelopmental, neurorescuing and lesion home-mediating GFs (vascular endothelial growth factor, hepatocyte growth factor, basic fibroblast growth factor), along with the active secretion of BDNF *in vivo*, were correlated with the activation of endogenous stem cells and striatal/nigral DAergic protection against neurodegeneration induced by 6-OHDA (Cova et al., 2010). Similarly, Park et al., using a MPTP mice model of PD, reported that BMSCs were able to modulate neurogenesis through the production of endothelium growth factor (Park et al., 2012).

In addition to the capability of BMSCs to induce survival and restorative effects on DAergic neurons, they also present immunomodulatory and anti-inflammatory properties. In this context, Danielyan and coworkers recently showed that intranasally delivered rat BMSCs to 6-OHDA exposed rats migrated toward the SN and the striatum, and prevented the decrease of DA in lesioned brain areas (Danielyan et al., 2011). Moreover, a substantial improvement of animals' motor function was also observed. These neuroprotective effects and functional recovery of the DAergic system have been associated with the increase of BDNF levels in the lesioned hemisphere side as well as with the BMSCs capacity to modulate the host immune response and exert a strong anti-inflammatory activity. Indeed, MSCs are known to modulate the response of inflammatory cells by decreasing the expression of pro-inflammatory cytokines, such as interleukin 1β, interleukin 2, interleukin 12, tumor necrosis factor α and interferon γ (Danielyan et al., 2011; Meirelles Lda et al., 2009). The secretion of interleukin-6, interleukin-10 and transforming growth factor β anti-inflammatory cytokines by BMSCs was also related with the protection of nigral DAergic neurons, by other authors (Kim et al., 2009).

Some other studies have also demonstrated that ASCs and WJ-MSCs secretome induces DAergic neurons survival in 6-OHDA models of PD, as well as an improvement in animals' motor impairments (McCoy et al., 2008; Weiss et al., 2006). For instance, Weiss et al. showed that WJ-MSCs transplantation in a 6-OHDA model of PD could increase the number of TH-positive cells and ameliorate PD animal behavior through the secretion of GDNF and fibroblast growth factor 20 (Weiss et al., 2006). Using the same animal model, McCoy et al. also demonstrated that intranigral transplantation of ASCs increased both the survival and protection of DAergic neurons in the lesioned area and ameliorated animals' motor deficits through the secretion of nerve growth factor, BDNF and GDNF (McCoy et al., 2008). The same authors also observed that ASCs attenuated microglial activation in the lesioned SNpc and suggested that this capacity to modulate microglial activity could be related with ASCs secretion of anti-inflamatory molecular mediators (McCoy et al., 2008).

From the above referred studies, it is clear that there is increasing evidence indicating that the neuroprotective and neuroregenerative effects of MSCs observed in PD are attributed to the secretion of soluble GFs and cytokines. MSCs secretion of these factors not only protects DAergic neurons from further degeneration and enhances endogenous reparative processes (*e.g.*, neurogenesis), but also acts as inflammation and immune response modulator. Moreover, recent reports have shown that besides soluble GFs and cytokines, MSCs also secrete microvesicles and exosomes containing miRNA, which are believed to mediate cell-to-cell communication and act as reparative agents (Baglio et al., 2012; Zhou et al., 2013b; Zhu et al., 2013). Indeed, Xin et al. have already demonstrated *in vitro* that exosomes secreted by BMSCs not only mediate communication with neurons and astrocytes, but could regulate neurite outgrowth by transferring miRNA (miR-133b) to neural cells (Xin et al., 2012).

6. Future perspectives

As reviewed by Onofrj and colleagues (Onofrj et al., 2008), satisfactory approaches that slow down PD, by protecting DAergic neurons from premature death, are missing.

As it was already described, the current symptomatic treatment relies in the reestablishment of dopamine levels through the use of L-DOPA, DA agonists (*e.g.*, ropinirole or pramipexole), MAO-B (*e.g.*, rasagiline or selegiline) and COMT (*e.g.*, entacapone or tolcapone) inhibitors, to compensate its deficits in the nigrostriatal dopaminergic pathway. Although efficacious, these molecules cannot induce the recovery of lost DAergic neurons or to protect those that have not yet been impacted by the disease (Onofrj et al., 2008). Moreover, it is nowadays accepted that several other factors contribute to PD progression besides DA deficits in the nigrostriatal pathway namely, mitochondrial dysfunction, reactive oxygen species, ubiquitination, proteasomal dysfunction and neuroinflammation (Yadav et al., 2014). This way, some questions should be raised: will there be alternative strategies to L-DOPA? Can we combine the use of L-DOPA with other therapeutic strategies to improve its action, and reduce side effects and dosages? Such questions represent at the present time one of the major challenges of PD research.

Safinamide ((*S*)-(+)-2-[4-(3-fluorbenzyloxybenzylamino)propanamide]methanesulfonate), a MAO-B inhibitor and a blocker of N-methyl-D-aspartate glutamate receptor (NMDAR) and sodium/calcium channels, has been presented as a promising therapeutic option for PD (Perez-Lloret and Rascol, 2016). Recently licensed by *European Medicines Agency* (EMA) as an "add-on" therapy, it has been described as an enhancer of dopaminergic transmission, presenting decreased secondary effects when compared to L-DOPA (Fabbri et al., 2015; Stocchi and Torti, 2016). In addition, neuroprotective effects have also been attributed to safinamide, preventing/inhibiting the formation of toxins or free radicals by oxidative stress and glutamate/gamma-aminobutyric acid (GABA) release, thereby reducing the excitotoxic input in DAergic neuronal death (Perez-Lloret and Rascol, 2016). From the application point of view, safinamide has already demonstrated to have a high oral bioavailability, presenting satisfactory levels of safety, tolerability and efficacy both in pre-clinical and clinical assays (Caccia et al., 2006; Fabbri et al., 2015). For instance, when compared to other MAO-B inhibitors like

selegiline or rasagiline, it revealed to be a potent modulator of DA, exhibiting a highly selective and reversible MAO-B inhibition, with a level of selectivity for MAO-B clearly superior to the above referred drugs (Caccia et al., 2006). Such evidence represents a crucial advantage, particularly for patients who experience adverse effects and need to be treated with other drugs, in which case the reversibility of safinamide avoids potential drug interactions. Also, when safinamide was added to a single DA agonist, a superior benefit was achieved (Stocchi et al., 2004). Even when combined with the standard treatment L-DOPA, safinamide was able to significantly increase its availability in the serum. This result suggests that such effect is accomplished by safinamide itself, due to the putative inhibition of DA reuptake through MAO-B inhibition and not due to the inhibition of metabolizing enzymes, such as dopadecarboxylase or catechol-*O*-methyltransferase (COMT) (Onofrj et al., 2008). Despite these promising results, to the best of our knowledge, there are no studies reporting the effects of safinamide in drug naïve patients and even in early stages of PD (Cattaneo et al., 2016; Fabbri et al., 2015; Muller, 2016). Such experiments could in the future open unprecedented opportunities to change PD research and its therapeutic approaches.

Along the same line as safinamide, there is opicapone, a novel, once-daily and potent third-generation cathecol-*O*-methyltransferase inhibitor (Ferreira et al., 2015a; Scott, 2016). Recently approved, oral opicapone is, like safinamide, an adjunct therapy to L-DOPA, to be used in adults with PD and end-of-dose motor fluctuations who cannot be stabilized (Devos and Moreau, 2015; Scott, 2016). Described as a hydrophilic 1,2,4-oxadiazole analog with pyridine N-oxide residue at position 3, this drug provides a high COMT inhibitory action, without inducing relevant cytotoxicity in cells (Kiss et al., 2010). Indeed, in pre-clinical models, opicapone was found to prolong the inhibitory effect on peripheral COMT and extend the bioavailability of L-DOPA, without inducing toxicity (Bonifacio et al., 2015). Similarly, on Cynomolgous monkeys, the referred drug was also found to not only increase the systemic exposure to L-DOPA, but also to increase its levels in the dorsal striatum and substantia nigra (Bonifacio et al., 2014). Even from the clinical point of view, Ferreira and colleagues (Ferreira et al., 2015b) demonstrated that opicapone significantly reduced COMT activity, increasing the systemic exposure to L-DOPA, which translated in an improved motor response by the patients, when compared to placebo. When it was applied in healthy volunteers, a pronounced effect was also observed in increasing L-DOPA bioavailability when compared to other COMT inhibitor, such as entacapone (Rocha et al., 2014). More recently, Ferreira and colleagues (Ferreira et al., 2015a) showed that a single take (daily) of opicapone could enable a simplified drug regimen, allowing for a decrease on the total daily L-DOPA dose and leading to an increase of dose intervals, thereby reducing the number of intakes and maximizing its benefits. Such evidence opens interesting new perspectives for PD treatment since, altogether, data suggests opicapone to be a promising alternative to the current available COMT inhibitors, simplifying PD drug regimens and increasing patient's quality of life (Fabbri et al., 2016).

In addition to these two promising drugs, there are also some new perspectives concerning DBS (Wichmann and DeLong, 2016). Indeed, it has been claimed that understanding how DBS could affect multiple cortical regions downstream, would be an important advance in its use as a therapeutic approach (Alhourani et al., 2015). Understanding also the network effects of DBS will allow tailoring the treatment based on biomarkers related to those effects. It is this way expected to achieve an increase on therapeutic efficacy and avoid undesirable side effects (Humphries and Gurney, 2012; Paek et al., 2015). Nevertheless, although promising, it still has some limitations, namely the inability to (totally) recover/protect DAergic neurons after PD onset. Therefore, the field's current view is that combinatory strategies may overcome the limitations of single drug/surgical approaches, particularly by combining them with stem cell-based strategies.

hMSCs secretome has recently been proposed as an alternative therapeutic tool for PD, given its ability to modulate DAergic neuronal survival (Teixeira et al., 2016a). In fact, using secretome as a therapeutic approach, rather than transplanting cells, would be a valuable tool in overcoming technical concerns associated to the latter (*e.g.*, number of cells needed and cell delivery). Recently it has been demonstrated that hMSCs secretome can be successfully modulated using dynamic culture conditions through computer-controlled bioreactors (Teixeira et al., 2016b). Also, some studies have shown that molecules secreted by hMSCs promote nervous tissue regeneration through activation/modulation of endogenous neuro-restorative processes. In the future, such molecules could be an efficacious add-on if combined with cell transplantation, pharmacological or surgical strategies (Buttery and Barker, 2014; Choi et al., 2010; Rowland et al., 2015; Yao et al., 2016). Although most of the available results support hMSCs secretome as a promising cell-free therapy and a potential *off-the-shelf* product for PD, current sources of MSCs do not allow for the isolation of a sufficient number of cells for their widespread clinical use, instead relying on invasive, expensive and labor–intense isolation protocols that yield MSCs with limited proliferative capacity (Teixeira et al., 2016b). Therefore, inducible pluripotent stem cells (iPSCs) have been suggested as a possible alternative source for obtaining large populations of MSC-like cells (iMSCs) (Jung et al., 2012; Kang et al., 2015). In fact, the use of iPSCs as a new possible therapeutic tool and also as a source of MSCs could be a breakthrough, since it yields a more homogenous population of MSCs, and probably is more robust in enhancing secretome production and potential. As recently assumed by Lian and colleagues (Lian et al., 2010), the greater potential of iPSCs and iMSCs may be related with their ability to survive and proliferate longer whether in culture or after transplantation, thereby being a more robust promising approach than the classical adult MSCs. Thus, the establishment of patient-specific iPSCs/iMSCs and their secretome could present an unprecedented opportunity to change PD research, by redefining the disease in its molecular and cellular basis.

iPSCs have also been proposed as a promising *in vitro* model that covers all the complexity of PD, allowing this way for research in many, if not all, of the features of this pathogenesis, either from sporadic or familial cases (Soldner et al., 2009). This approach may also allow to predict (new) therapeutic outcomes for experimental PD treatments, alone or in combination (*e.g.*, PD drugs, DBS or iMSCs/iPSCs secretome), as well as to track PD progression through the identification of new therapeutical targets. This way maybe one day we might understand how to prevent or slow down degeneration of DAergic neurons.

7. Conclusions

PD is the second most prevalent neurodegenerative disorder, characterized by a variety of motor and non-motor features. With the significant advances made in the fields of etiology, pathobiology and patho-anatomy of PD, new pharmacologic agents, gene engineering and cell replacement therapeutic approaches have been developed to meet the clinical challenge of treating or modifying the course of the disease. Although important progresses have been achieved, there are still important gaps missing, particularly on better methods to induce regenerative processes in the areas affected by the disease. In order to overcome this, in the future it will be important to understand the true potential of emerging technologies, such as those derived from iPSC or MSCs secretome, as well as how these may be combined with existing molecular and pharmacotherapies. Doing so, it will

be possible to tackle PD in a multi-dimensional and more effective way.

Acknowledgments

Portuguese Foundation for Science and Technology (FCT) for the PhD fellowship attributed to A.O. Pires (Reference: SFRH/BD/33900/2009) and the IF development grant to A.J. Salgado (Reference: IF/00111/2013). Project NORTE-01-0145-FEDER-000013, supported by the Northern Portugal Regional Operational Programme (NORTE 2020), under the Portugal 2020 Partnership Agreement, through the European Regional Development Fund (FEDER). Funded by FEDER funds, through the Competitiveness Factors Operational Programme (COMPETE), and by National funds, through the Foundation for Science and Technology (FCT), under the scope of the project POCI-01-0145-FEDER-007038.

References

Ai, Y., Markesbery, W., Zhang, Z., Grondin, R., Elseberry, D., Gerhardt, G.A., Gash, D. M., 2003. Intraputamenal infusion of GDNF in aged rhesus monkeys: distribution and dopaminergic effects. J. Comp. Neurol. 461, 250–261.

Akao, Y., Maruyama, W., Yi, H., Shamoto-Nagai, M., Youdim, M.B., Naoi, M., 2002. An anti-Parkinson's disease drug, N-propargyl-1(R)-aminoindan (rasagiline), enhances expression of anti-apoptotic bcl-2 in human dopaminergic SH-SY5Y cells. Neurosci. Lett. 326, 105–108.

Alexander, G.E., Crutcher, M.D., DeLong, M.R., 1990. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, “prefrontal” and “limbic” functions. Prog. Brain Res. 85, 119–146.

Alhourani, A., McDowell, M.M., Randazzo, M.J., Wozny, T.A., Kondylis, E.D., Lipski, W. J., Beck, S., Karp, J.F., Ghuman, A.S., Richardson, R.M., 2015. Network effects of deep brain stimulation. J. Neurophysiol. 114, 2105–2117.

Amalric, M., Lopez, S., Goudet, C., Fisone, G., Battaglia, G., Nicoletti, F., Pin, J.P., Acher, F.C., 2013. Group III and subtype 4 metabotropic glutamate receptor agonists: discovery and pathophysiological applications in Parkinson's disease. Neuropharmacology 66, 53–64.

Anderson, V.C., Burchiel, K.J., Hogarth, P., Favre, J., Hammerstad, J.P., 2005. Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. Arch. Neurol. 62, 554–560.

Aosaki, T., Miura, M., Suzuki, T., Nishimura, K., Masuda, M., 2010. Acetylcholine-dopamine balance hypothesis in the striatum: an update. Geriatr. Gerontol. Int. 10 (Suppl. 1), S148–S157.

Azari, M.F., Mathias, L., Ozturk, E., Cram, D.S., Boyd, R.L., Petratos, S., 2010. Mesenchymal stem cells for treatment of CNS injury. Curr. Neuropharmacol. 8, 316–323.

Aziz, T.Z., Peggs, D., Sambrook, M.A., Crossman, A.R., 1991. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. Mov. Disord. 6, 288–292.

Baer, P.C., Geiger, H., 2012. Adipose-derived mesenchymal stromal/stem cells: tissue localization, characterization, and heterogeneity. Stem Cells Int. 2012, 1–11.

Baglio, S.R., Pegtel, D.M., Baldini, N., 2012. Mesenchymal stem cell secreted vesicles provide novel opportunities in (stem) cell-free therapy. Front. Physiol. 3, 1–11.

Bankiewicz, K.S., Daadi, M., Pivirotto, P., Bringas, J., Sanftner, L., Cunningham, J., Forsayeth, J.R., Eberling, J.L., 2006. Focal striatal dopamine may potentiate dyskinesias in parkinsonian monkeys. Exp. Neurol. 197, 363–372.

Bankiewicz, K.S., Eberling, J.L., Kohutnicka, M., Jagust, W., Pivirotto, P., Bringas, J., Cunningham, J., Budinger, T.F., Harvey-White, J., 2000. Convection-enhanced delivery of AAV vector in parkinsonian monkeys; in vivo detection of gene expression and restoration of dopaminergic function using pro-drug approach. Exp. Neurol. 164, 2–14.

Bar Am, O., Amit, T., Youdim, M.B., 2004. Contrasting neuroprotective and neurotoxic actions of respective metabolites of anti-Parkinson drugs rasagiline and selegiline. Neurosci. Lett. 355, 169–172.

Bartus, R.T., Herzog, C.D., Chu, Y., Wilson, A., Brown, L., Siffert, J., Johnson Jr., E.M., Olanow, C.W., Mufson, E.J., Kordower, J.H., 2011. Bioactivity of AAV2-neurturin gene therapy (CERE-120): differences between Parkinson's disease and nonhuman primate brains. Mov. Disord. 26, 27–36.

Battaglia, G., Busceti, C.L., Molinaro, G., Biagioni, F., Traficante, A., Nicoletti, F., Bruno, V., 2006. Pharmacological activation of mGlu4 metabotropic glutamate receptors reduces nigrostriatal degeneration in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. J. Neurosci. 26, 7222–7229.

Beach, T.G., Adler, C.H., Sue, L.I., Peirce, J.B., Bachalakuri, J., Dalsing-Hernandez, J.E., Lue, L.F., Caviness, J.N., Connor, D.J., Sabbagh, M.N., Walker, D.G., 2008. Reduced striatal tyrosine hydroxylase in incidental Lewy body disease. Acta Neuropathol. 115, 445–451.

Ben-Hur, T., Idelson, M., Khaner, H., Pera, M., Reinhartz, E., Itzik, A., Reubinoff, B.E., 2004. Transplantation of human embryonic stem cell-derived neural progenitors improves behavioral deficit in Parkinsonian rats. Stem Cells 22, 1246–1255.

Benabid, A.L., Chabardes, S., Mitrofanis, J., Pollak, P., 2009a. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol. 8, 67–81.

Benabid, A.L., Chabardes, S., Torres, N., Piallat, B., Krack, P., Fraix, V., Pollak, P., 2009b. Functional neurosurgery for movement disorders: a historical perspective. Prog. Brain Res. 175, 379–391.

Bennett, L., Yang, M., Enikolopov, G., Iacovitti, L., 2009. Circumventricular organs: a novel site of neural stem cells in the adult brain. Mol. Cell. Neurosci. 41, 337–347.

Bennouar, K.E., Uberti, M.A., Melon, C., Bacolod, M.D., Jimenez, H.N., Cajina, M., Kerkerian-Le Goff, L., Doller, D., Gubellini, P., 2013. Synergy between L-DOPA and a novel positive allosteric modulator of metabotropic glutamate receptor 4: implications for Parkinson's disease treatment and dyskinesia. Neuropharmacology 66, 158–169.

Benskey, M.J., Perez, R.G., Manfredsson, F.P., 2016. The contribution of alpha synuclein to neuronal survival and function implications for Parkinson's disease. J. Neurochem. 3, 331–359.

Bergman, H., Wichmann, T., DeLong, M.R., 1990. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 249, 1436–1438.

Bernheimer, H., Birkmayer, W., Hornykiewicz, O., 1962. Behavior of monoamine oxidase in the brain of man after therapy with monoamine oxidase inhibitors. Wien. Klin. Wochenschr. 74, 558–559.

Betts, M.J., O'Neill, M.J., Duty, S., 2012. Allosteric modulation of the group III mGlu(4) receptor provides functional neuroprotection in the 6-hydroxydopamine rat model of Parkinson's disease. Br. J. Pharmacol. 166, 2317–2330.

Beurrier, C., Lopez, S., Revy, D., Selvam, C., Goudet, C., Lherondel, M., Gubellini, P., Kerkerian-LeGoff, L., Acher, F., Pin, J.P., Amalric, M., 2009. Electrophysiological and behavioral evidence that modulation of metabotropic glutamate receptor 4 with a new agonist reverses experimental parkinsonism. FASEB J. 23, 3619–3628.

Björklund, A., Kordower, J.H., 2013. Cell therapy for Parkinson's disease: what next? Mov. Disord. 28, 110–115.

Björklund, A., Schmidt, R.H., Stenevi, U., 1980. Functional reinnervation of the neostriatum in the adult rat by use of intraparenchymal grafting of dissociated cell suspensions from the substantia nigra. Cell Tissue Res. 212, 39–45.

Björklund, L.M., Sanchez-Pernaute, R., Chung, S., Andersson, T., Chen, I.Y., McNaught, K.S., Brownell, A.L., Jenkins, B.G., Wahlestedt, C., Kim, K.S., Isacson, O., 2002. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proc. Natl. Acad. Sci. U. S. A. 99, 2344–2349.

Björklund, T., Carlsson, T., Cederfjall, E.A., Carta, M., Kirik, D., 2010. Optimized adeno-associated viral vector-mediated striatal DOPA delivery restores sensorimotor function and prevents dyskinesias in a model of advanced Parkinson's disease. Brain 133, 496–511.

Blandini, F., Cova, L., Armentero, M.T., Zennaro, E., Levandis, G., Bossolasco, P., Calzarossa, C., Mellone, M., Giuseppe, B., Deliliers, G.L., Polli, E., Nappi, G., Silani, V., 2010. Transplantation of undifferentiated human mesenchymal stem cells protects against 6-hydroxydopamine neurotoxicity in the rat. Cell Transplant. 19, 203–217.

Bonifacio, M.J., Sutcliffe, J.S., Torrao, L., Wright, L.C., Soares-da-Silva, P., 2014. Brain and peripheral pharmacokinetics of levodopa in the cynomolgus monkey following administration of opicapone, a third generation nitrocatechol COMT inhibitor. Neuropharmacology 77, 334–341.

Bonifacio, M.J., Torrao, L., Loureiro, A.I., Palma, P.N., Wright, L.C., Soares-da-Silva, P., 2015. Pharmacological profile of opicapone, a third-generation nitrocatechol catechol-O-methyl transferase inhibitor, in the rat. Br. J. Pharmacol. 172, 1739–1752.

Bonnamain, V., Neveu, I., Naveilhan, P., 2012. Neural stem/progenitor cells as a promising candidate for regenerative therapy of the central nervous system. Front. Cell Neurosci. 6, 17.

Bouchez, G., Sensebe, L., Vourc'h, P., Garreau, L., Bodard, S., Rico, A., Guilloteau, D., Charbord, P., Besnard, J.C., Chalon, S., 2008. Partial recovery of dopaminergic pathway after graft of adult mesenchymal stem cells in a rat model of Parkinson's disease. Neurochem. Int. 52, 1332–1342.

Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen Steur, E.N., Braak, E., 2003a. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211.

Braak, H., Rub, U., Gai, W.P., Del Tredici, K., 2003b. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J. Neural Transm. (Vienna) 110, 517–536.

Bras, J.M., Singleton, A., 2009. Genetic susceptibility in Parkinson's disease. Biochim. Biophys. Acta 1792, 597–603.

Brederlau, A., Correia, A.S., Anisimov, S.V., Elmi, M., Paul, G., Roybon, L., Morizane, A., Bergquist, F., Riebe, I., Nannmark, U., Carta, M., Hanse, E., Takahashi, J., Sasai, Y., Funa, K., Brundin, P., Eriksson, P.S., Li, J.Y., 2006. Transplantation of human embryonic stem cell-derived cells to a rat model of Parkinson's disease: effect of in vitro differentiation on graft survival and teratoma formation. Stem Cells 24, 1433–1440.

Brundin, P., Barker, R.A., Parmar, M., 2010. Neural grafting in Parkinson's disease problems and possibilities. Prog. Brain Res. 184, 265–294.

Buttery, P.C., Barker, R.A., 2014. Treating Parkinson's disease in the 21st century: can stem cell transplantation compete? J. Comp. Neurol. 522, 2802–2816.

Caccia, C., Maj, R., Calabresi, M., Maestroni, S., Faravelli, L., Curatolo, L., Salvati, P., Fariello, R.G., 2006. Safinamide: from molecular targets to a new anti-Parkinson drug. Neurology 67, S18–S23.

Caiazzo, M., Dell'Anno, M.T., Dvoretskova, E., Lazarevic, D., Taverna, S., Leo, D., Sotnikova, T.D., Menegon, A., Roncaglia, P., Colciago, G., Russo, G., Carninci, P., Pezzoli, G., Gainetdinov, R.R., Gustincich, S., Dityatev, A., Broccoli, V., 2011. Direct generation of functional dopaminergic neurons from mouse and human fibroblasts. Nature 476, 224–227.
Caplan, A.I., 1991. Mesenchymal stem cells. J. Orthop. Res. 9, 641–650.
Caplan, A.I., Dennis, J.E., 2006. Mesenchymal stem cells as trophic mediators. J. Cell. Biochem. 98, 1076–1084.
Cartmell, J., Schoepp, D.D., 2000. Regulation of neurotransmitter release by metabotropic glutamate receptors. J. Neurochem. 75, 889–907.
Carvey, P.M., Ling, Z.D., Sortwell, C.E., Pitzer, M.R., McGuire, S.O., Storch, A., Collier, T. J., 2001. A clonal line of mesencephalic progenitor cells converted to dopamine neurons by hematopoietic cytokines: a source of cells for transplantation in Parkinson's disease. Exp. Neurol. 171, 98–108.
Cattaneo, C., Sardina, M., Bonizzoni, E., 2016. Safinamide as add-on therapy to levodopa in mid- to late-stage Parkinson's disease fluctuating patients: post hoc analyses of studies 016 and SETTLE. J. Parkinsons Dis. 6, 165–173.
Celanire, S., Campo, B., 2012. Recent advances in the drug discovery of metabotropic glutamate receptor 4 (mGluR4) activators for the treatment of CNS and non-CNS disorders. Expert Opin. Drug Discov. 7, 261–280.
Chao, Y.X., He, B.P., Tay, S.S., 2009. Mesenchymal stem cell transplantation attenuates blood brain barrier damage and neuroinflammation and protects dopaminergic neurons against MPTP toxicity in the substantia nigra in a model of Parkinson's disease. J. Neuroimmunol. 216, 39–50.
Charcot, J.M., 2002. Policlinique du Mardi 31 Janvier. Charcot J-M Leçons du mardi à la Saltpêtrière. La Bibliothèque des Introuvables, Paris, pp. 199–220.
Chen, J., Li, Y., Chopp, M., 2000. Intracerebral transplantation of bone marrow with BDNF after MCAo in rat. Neuropharmacology 39, 711–716.
Chen, J., Li, Y., Wang, L., Zhang, Z., Lu, D., Lu, M., Chopp, M., 2001a. Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. Stroke 32, 1005–1011.
Chen, J., Sanberg, P.R., Li, Y., Wang, L., Lu, M., Willing, A.E., Sanchez-Ramos, J., Chopp, M., 2001b. Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats. Stroke 32, 2682–2688.
Chen, L., Ding, Y., Cagniard, B., Van Laar, A.D., Mortimer, A., Chi, W., Hastings, T.G., Kang, U.J., Zhuang, X., 2008. Unregulated cytosolic dopamine causes neurodegeneration associated with oxidative stress in mice. J. Neurosci. 28, 425–433.
Cheng, H.C., Ulane, C.M., Burke, R.E., 2010. Clinical progression in Parkinson disease and the neurobiology of axons. Ann. Neurol. 67, 715–725.
Cho, M.S., Lee, Y.E., Kim, J.Y., Chung, S., Cho, Y.H., Kim, D.S., Kang, S.M., Lee, H., Kim, M. H., Kim, J.H., Leem, J.W., Oh, S.K., Choi, Y.M., Hwang, D.Y., Chang, J.W., Kim, D.W., 2008. Highly efficient and large-scale generation of functional dopamine neurons from human embryonic stem cells. Proc. Natl. Acad. Sci. U. S. A. 105, 3392–3397.
Choi, Y.J., Li, W.Y., Moon, G.J., Lee, P.H., Ahn, Y.H., Lee, G., Bang, O.Y., 2010. Enhancing trophic support of mesenchymal stem cells by ex vivo treatment with trophic factors. J. Neurol. Sci. 298, 28–34.
Christine, C.W., Starr, P.A., Larson, P.S., Eberling, J.L., Jagust, W.J., Hawkins, R.A., VanBrocklin, H.F., Wright, J.F., Bankiewicz, K.S., Aminoff, M.J., 2009. Safety and tolerability of putaminal AADC gene therapy for Parkinson disease. Neurology 73, 1662–1669.
Clark, J., Clore, E.L., Zheng, K., Adame, A., Masliah, E., Simon, D.K., 2010. Oral N-acetyl-cysteine attenuates loss of dopaminergic terminals in alpha-synuclein overexpressing mice. PLoS ONE 5, e12333.
Connolly, B.S., Lang, A.E., 2014. Pharmacological treatment of Parkinson disease: a review. JAMA 311, 1670–1683.
Cooper, I.S., 1973. Effect of chronic stimulation of anterior cerebellum on neurological disease. Lancet 1, 206.
Coune, P.G., Schneider, B.L., Aebischer, P., 2012. Parkinson's disease: gene therapies. Cold Spring Harb. Perspect. Med. 2, a009431.
Cova, L., Armentero, M.T., Zennaro, E., Calzarossa, C., Bossolasco, P., Busca, G., Lambertenghi Deliliers, G., Polli, E., Nappi, G., Silani, V., Blandini, F., 2010. Multiple neurogenic and neurorescue effects of human mesenchymal stem cell after transplantation in an experimental model of Parkinson's disease. Brain Res. 1311, 12–27.
Cummins, G., Barker, R.A., 2012. What is the most promising treatment for Parkinson's disease: genes, cells, growth factors or none of the above? Regen. Med. 7, 617–621.
Cyr, M., Beaulieu, J.M., Laakso, A., Sotnikova, T.D., Yao, W.D., Bohn, L.M., Gainetdinov, R.R., Caron, M.G., 2003. Sustained elevation of extracellular dopamine causes motor dysfunction and selective degeneration of striatal GABAergic neurons. Proc. Natl. Acad. Sci. U. S. A. 100, 11035–11040.
Danielyan, L., Schafer, R., von Ameln-Mayerhofer, A., Bernhard, F., Verleysdonk, S., Buadze, M., Lourhmati, A., Klopfer, T., Schaumann, F., Schmid, B., Koehle, C., Proksch, B., Weissert, R., Reichardt, H.M., van den Brandt, J., Buniatian, G.H., Schwab, M., Gleiter, C.H., Frey II, W.H., 2011. Therapeutic efficacy of intranasally delivered mesenchymal stem cells in a rat model of Parkinson disease. Rejuvenation Res. 14, 3–16.
Dauer, W., Przedborski, S., 2003. Parkinson's disease: mechanisms and models. Neuron 39, 889–909.
Dawson, T.M., Dawson, V.L., 2003. Molecular pathways of neurodegeneration in Parkinson's disease. Science 302, 819–822.
Devos, D., Moreau, C., 2015. Opicapone for motor fluctuations in Parkinson's disease. Lancet Neurol..
Dewey Jr., R.B., Hutton, J.T., LeWitt, P.A., Factor, S.A., 2001. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. Arch. Neurol. 58, 1385–1392.
Dexter, D.T., Jenner, P., 2013. Parkinson disease: from pathology to molecular disease mechanisms. Free Radic. Biol. Med. 62, 132–144.
Di Monte, D.A., 2003. The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? Lancet Neurol. 2, 531–538.
Dickson, D.W., Braak, H., Duda, J.E., Duyckaerts, C., Gasser, T., Halliday, G.M., Hardy, J., Leverenz, J.B., Del Tredici, K., Wszolek, Z.K., Litvan, I., 2009. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. Lancet Neurol. 8, 1150–1157.
Ding, D.C., Shyu, W.C., Chiang, M.F., Lin, S.Z., Chang, Y.C., Wang, H.J., Su, C.Y., Li, H., 2007. Enhancement of neuroplasticity through upregulation of beta1-integrin in human umbilical cord-derived stromal cell implanted stroke model. Neurobiol. Dis. 27, 339–353.
Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., Deans, R., Keating, A., Prockop, D., Horwitz, E., 2006. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8, 315–317.
Dunkel, P., Chai, C.L., Sperlagh, B., Huleatt, P.B., Matyus, P., 2012. Clinical utility of neuroprotective agents in neurodegenerative diseases: current status of drug development for Alzheimer's, Parkinson's and Huntington's diseases, and amyotrophic lateral sclerosis. Expert Opin. Investig. Drugs 21, 1267–1308.
Dunnett, S.B., Bjorklund, A., Schmidt, R.H., Stenevi, U., Iversen, S.D., 1983. Intracerebral grafting of neuronal cell suspensions. V. Behavioural recovery in rats with bilateral 6-OHDA lesions following implantation of nigral cell suspensions. Acta Physiol. Scand. Suppl. 522, 39–47.
Dunnett, S.B., Hernandez, T.D., Summerfield, A., Jones, G.H., Arbuthnott, G., 1988. Graft-derived recovery from 6-OHDA lesions: specificity of ventral mesencephalic graft tissues. Exp. Brain Res. 71, 411–424.
Eaves, C.J., Cashman, J.D., Sutherland, H.J., Otsuka, T., Humphries, R.K., Hogge, D.E., Lansdorp, P.L., Eaves, A.C., 1991. Molecular analysis of primitive hematopoietic cell proliferation control mechanisms. Ann. N. Y. Acad. Sci. 628, 298–306.
Eggert, D., Dash, P.K., Gorantla, S., Dou, H., Schifitto, G., Maggirwar, S.B., Dewhurst, S., Poluektova, L., Gelbard, H.A., Gendelman, H.E., 2010. Neuroprotective activities of CEP-1347 in models of neuroAIDS. J. Immunol. 184, 746–756.
Ehringer, H., Hornykiewicz, O., 1960. Verteilung von noradrenalin and dopamin im gehirn des menschen und ihr verhalten bei erkrankungen des extrapyramidalen systems. Klin. Wschr. 38, 1126–1239.
Ehringer, H., Hornykiewicz, O., 1998. Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. Parkinsonism Relat. Disord. 4, 53–57.
Emborg, M.E., Carbon, M., Holden, J.E., During, M.J., Ma, Y., Tang, C., Moirano, J., Fitzsimons, H., Roitberg, B.Z., Tuccar, E., Roberts, A., Kaplitt, M.G., Eidelberg, D., 2007. Subthalamic glutamic acid decarboxylase gene therapy: changes in motor function and cortical metabolism. J. Cereb. Blood Flow Metab. 27, 501–509.
Emsley, J.G., Mitchell, B.D., Kempermann, G., Macklis, J.D., 2005. Adult neurogenesis and repair of the adult CNS with neural progenitors, precursors, and stem cells. Prog. Neurobiol. 75, 321–341.
Fabbri, M., Rosa, M.M., Abreu, D., Ferreira, J.J., 2015. Clinical pharmacology review of safinamide for the treatment of Parkinson's disease. Neurodegener. Dis. Manag. 5, 481–496.
Fabbri, M., Rosa, M.M., Ferreira, J.J., 2016. Clinical pharmacology review of opicapone for the treatment of Parkinson's disease. Neurodegener. Dis. Manag. 6, 349–362.
Factor, S.A., 2008. Current status of symptomatic medical therapy in Parkinson's disease. Neurotherapeutics 5, 164–180.
Parkinson's Disease Diagnosis and Clinical Management. In: Factor, S.A., Weiner, W. J. (Eds.), Demos, New York.
Faggiani, E., Benazzouz, A., 2016. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: from history to the interaction with the monoaminergic systems. Prog. Neurobiol..
Fernandez, H.H., Chen, J.J., 2007. Monamine oxidase inhibitors: current and emerging agents for Parkinson disease. Clin. Neuropharmacol. 30, 150–168.
Ferraye, M.U., Debu, B., Fraix, V., Goetz, L., Ardouin, C., Yelnik, J., Henry-Lagrange, C., Seigneuret, E., Piallat, B., Krack, P., Le Bas, J.F., Benabid, A.L., Chabardes, S., Pollak, P., 2010. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain 133, 205–214.
Ferreira, J.J., Lees, A., Rocha, J.F., Poewe, W., Rascol, O., Soares-da-Silva, P., Bi-Park, i., 2015a. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. Lancet Neurol..
Ferreira, J.J., Rascol, O., 2000. Prevention and therapeutic strategies for levodopa-induced dyskinesias in Parkinson's disease. Curr. Opin. Neurol. 13, 431–436.
Ferreira, J.J., Rocha, J.F., Falcao, A., Santos, A., Pinto, R., Nunes, T., Soares-da-Silva, P., 2015b. Effect of opicapone on levodopa pharmacokinetics, catechol-O-methyltransferase activity and motor fluctuations in patients with Parkinson's disease. Eur. J. Neurol. 22, 815–825 e856.
Follett, K.A., Weaver, F.M., Stern, M., Hur, K., Harris, C.L., Luo, P., Marks Jr., W.J., Rothlind, J., Sagher, O., Moy, C., Pahwa, R., Burchiel, K., Hogarth, P., Lai, E.C., Duda, J.E., Holloway, K., Samii, A., Horn, S., Bronstein, J.M., Stoner, G., Starr, P.A., Simpson, R., Baltuch, G., De Salles, A., Huang, G.D., Reda, D.J., 2010. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N. Engl. J. Med. 362, 2077–2091.
Freed, C.R., Greene, P.E., Breeze, R.E., Tsai, W.Y., DuMouchel, W., Kao, R., Dillon, S., Winfield, H., Culver, S., Trojanowski, J.Q., Eidelberg, D., Fahn, S., 2001.

Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N. Engl. J. Med. 344, 710–719.
Friedenstein, A.J., Chailakhyan, R.K., Latsinik, N.V., Panasyuk, A.F., Keiliss-Borok, I.V., 1974. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning in vitro and retransplantation in vivo. Transplantation 17, 331–340.
Gibson, S.A., Gao, G.D., McDonagh, K., Shen, S., 2012. Progress on stem cell research towards the treatment of Parkinson's disease. Stem Cell Res. Ther. 3, 1–10.
Giladi, N., McDermott, M.P., Fahn, S., Przedborski, S., Jankovic, J., Stern, M., Tanner, C., 2001. Freezing of gait in PD: prospective assessment in the DATATOP cohort. Neurology 56, 1712–1721.
Gjerloff, T., Fedorova, T., Knudsen, K., Munk, O.L., Nahimi, A., Jacobsen, S., Danielsen, E.H., Terkelsen, A.J., Hansen, J., Pavese, N., Brooks, D.J., Borghammer, P., 2015. Imaging acetylcholinesterase density in peripheral organs in Parkinson's disease with 11C-donepezil PET. Brain 138, 653–663.
Gjerstad, M.D., Alves, G., Wentzel-Larsen, T., Aarsland, D., Larsen, J.P., 2006. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? Neurology 67, 853–858.
Gjerstad, M.D., Wentzel-Larsen, T., Aarsland, D., Larsen, J.P., 2007. Insomnia in Parkinson's disease: frequency and progression over time. J. Neurol. Neurosurg. Psychiatry 78, 476–479.
Grondin, R., Cass, W.A., Zhang, Z., Stanford, J.A., Gash, D.M., Gerhardt, G.A., 2003. Glial cell line-derived neurotrophic factor increases stimulus-evoked dopamine release and motor speed in aged rhesus monkeys. J. Neurosci. 23, 1974–1980.
Grondin, R., Zhang, Z., Yi, A., Cass, W.A., Maswood, N., Andersen, A.H., Elsberry, D.D., Klein, M.C., Gerhardt, G.A., Gash, D.M., 2002. Chronic, controlled GDNF infusion promotes structural and functional recovery in advanced parkinsonian monkeys. Brain 125, 2191–2201.
Group, P.S., 2005a. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch. Neurol. 62, 241–248.
Group, T.P.S., 2005b. Safety and Efficacy Study of CEP-1347 in the Treatment of Parkinson's Disease. .
Hadaczek, P., Wu, G., Sharma, N., Ciesielska, A., Bankiewicz, K., Davidow, A.L., Lu, Z. H., Forsayeth, J., Ledeen, R.W., 2015. GDNF signaling implemented by GM1 ganglioside; failure in Parkinson's disease and GM1-deficient murine model. Exp. Neurol. 263, 177–189.
Hagell, P., Schrag, A., Piccini, P., Jahanshahi, M., Brown, R., Rehncrona, S., Widner, H., Brundin, P., Rothwell, J.C., Odin, P., Wenning, G.K., Morrish, P., Gustavii, B., Bjorklund, A., Brooks, D.J., Marsden, C.D., Quinn, N.P., Lindvall, O., 1999. Sequential bilateral transplantation in Parkinson's disease: effects of the second graft. Brain 122, 1121–1132.
Hargus, G., Cooper, O., Deleidi, M., Levy, A., Lee, K., Marlow, E., Yow, A., Soldner, F., Hockemeyer, D., Hallett, P.J., Osborn, T., Jaenisch, R., Isacson, O., 2010. Differentiated Parkinson patient-derived induced pluripotent stem cells grow in the adult rodent brain and reduce motor asymmetry in Parkinsonian rats. Proc. Natl. Acad. Sci. U. S. A. 107, 15921–15926.
Harikrishna Reddy, D., Misra, S., Medhi, B., 2014. Advances in drug development for Parkinson's disease: present status. Pharmacology 93, 260–271.
Hart, R.G., Pearce, L.A., Ravina, B.M., Yaltho, T.C., Marler, J.R., 2009. Neuroprotection trials in Parkinson's disease: systematic review. Mov. Disord. 24, 647–654.
Hauser, R.A., 2011. Future treatments for Parkinson's disease: surfing the PD pipeline. Int. J. Neurosci. 121 (Suppl. 2), 53–62.
Hayashi, T., Wakao, S., Kitada, M., Ose, T., Watabe, H., Kuroda, Y., Mitsunaga, K., Matsuse, D., Shigemoto, T., Ito, A., Ikeda, H., Fukuyama, H., Onoe, H., Tabata, Y., Dezawa, M., 2013. Autologous mesenchymal stem cell-derived dopaminergic neurons function in parkinsonian macaques. J. Clin. Invest. 123, 272–284.
Heikkinen, H., Varhe, A., Laine, T., Puttonen, J., Kela, M., Kaakkola, S., Reinikainen, K., 2002. Entacapone improves the availability of L-DOPA in plasma by decreasing its peripheral metabolism independent of L-DOPA/carbidopa dose. Br. J. Clin. Pharmacol. 54, 363–371.
Hely, M.A., Morris, J.G., Reid, W.G., Trafficante, R., 2005. Sydney Multicenter Study of Parkinson's disease: non-L-DOPA-responsive problems dominate at 15 years. Mov. Disord. 20, 190–199.
Hermann, A., Gastl, R., Liebau, S., Popa, M.O., Fiedler, J., Boehm, B.O., Maisel, M., Lerche, H., Schwarz, J., Brenner, R., Storch, A., 2004. Efficient generation of neural stem cell-like cells from adult human bone marrow stromal cells. J. Cell Sci. 117, 4411–4422.
Herrero, M.T., Pérez-Otaño, I., Oset, C., Kastner, A., Hirsch, E.C., Agid, Y., Luquin, M.R., Obeso, J.A., Río, J.D., 1993. GM-1 ganglioside promotes the recovery of surviving midbrain dopaminergic neurons in MPTP-treated monkeys. Neuroscience 56 (4), 965–972.
Herzog, C.D., Dass, B., Gasmi, M., Bakay, R., Stansell, J.E., Tuszynski, M., Bankiewicz, K., Chen, E.Y., Chu, Y., Bishop, K., Kordower, J.H., Bartus, R.T., 2008. Transgene expression, bioactivity, and safety of CERE-120 (AAV2-neurturin) following delivery to the monkey striatum. Mol. Ther. 16, 1737–1744.
Herzog, C.D., Dass, B., Holden, J.E., Stansell III, J., Gasmi, M., Tuszynski, M.H., Bartus, R.T., Kordower, J.H., 2007. Striatal delivery of CERE-120, an AAV2 vector encoding human neurturin, enhances activity of the dopaminergic nigrostriatal system in aged monkeys. Mov. Disord. 22, 1124–1132.
Holmay, M.J., Terpstra, M., Coles, L.D., Mishra, U., Ahlskog, M., Oz, G., Cloyd, J.C., Tuite, P.J., 2013. N-Acetylcysteine boosts brain and blood glutathione in Gaucher and Parkinson diseases. Clin. Neuropharmacol. 36, 103–106.
Hu, S.L., Luo, H.S., Li, J.T., Xia, Y.Z., Li, L., Zhang, L.J., Meng, H., Cui, G.Y., Chen, Z., Wu, N., Lin, J.K., Zhu, G., Feng, H., 2010. Functional recovery in acute traumatic spinal cord injury after transplantation of human umbilical cord mesenchymal stem cells. Crit. Care Med. 38, 2181–2189.
Humphries, M.D., Gurney, K., 2012. Network effects of subthalamic deep brain stimulation drive a unique mixture of responses in basal ganglia output. Eur. J. Neurosci. 36, 2240–2251.
Jankovic, J., 2008. Parkinson's disease: clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry 79, 368–376.
Jankovic, J., Cardoso, F., Grossman, R.G., Hamilton, W.J., 1995. Outcome after stereotactic thalamotomy for parkinsonian, essential, and other types of tremor. Neurosurgery 37, 680–686 (discussion 686–687).
Jankovic, J., 2016. Movement disorders in 2016: Progress in Parkinson disease and other movement disorders. Nat. Rev. Neurol. 13 (2), 76–78.
Jenner, P., 2003. Oxidative stress in Parkinson's disease. Ann. Neurol. 53 (Suppl 3), S26–S36 (discussion S36–28).
Jenner, P., 2004. Preclinical evidence for neuroprotection with monoamine oxidase-B inhibitors in Parkinson's disease. Neurology 63, S13–S22.
Jenner, P., 2007. Oxidative stress and Parkinson's disease. Handb. Clin. Neurol. 83, 507–520.
Jiang, Y., Jahagirdar, B.N., Reinhardt, R.L., Schwartz, R.E., Keene, C.D., Ortiz-Gonzalez, X.R., Reyes, M., Lenvik, T., Lund, T., Blackstad, M., Du, J., Aldrich, S., Lisberg, A., Low, W.C., Largaespada, D.A., Verfaillie, C.M., 2002. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 418, 41–49.
Jost, W.H., Friede, M., Schnitker, J., 2012. Indirect meta-analysis of randomised placebo-controlled clinical trials on rasagiline and selegiline in the symptomatic treatment of Parkinson's disease. Basal Ganglia 2, S17–S26.
Jost, W.H., Friede, M., Schnitker, J., 2014. Comparative efficacy of selegiline versus rasagiline in the treatment of early Parkinson's disease. Eur. Rev. Med. Pharmacol. Sci. 18, 3349.
Jung, Y., Bauer, G., Nolta, J.A., 2012. Concise review: induced pluripotent stem cell-derived mesenchymal stem cells: progress toward safe clinical products. Stem Cells 30, 42–47.
Kalia, L.V., Brotchie, J.M., Fox, S.H., 2013. Novel nondopaminergic targets for motor features of Parkinson's disease: review of recent trials. Mov. Disord. 28, 131–144.
Kalinderi, K., Fidani, L., Katsarou, Z., Bostantjopoulou, S., 2011. Pharmacological treatment and the prospect of pharmacogenetics in Parkinson's disease. Int. J. Clin. Pract. 65, 1289–1294.
Kang, R., Zhou, Y., Tan, S., Zhou, G., Aagaard, L., Xie, L., Bunger, C., Bolund, L., Luo, Y., 2015. Mesenchymal stem cells derived from human induced pluripotent stem cells retain adequate osteogenicity and chondrogenicity but less adipogenicity. Stem Cell Res. Ther. 6, 144.
Kaplitt, M.G., Feigin, A., Tang, C., Fitzsimons, H.L., Mattis, P., Lawlor, P.A., Bland, R.J., Young, D., Strybing, K., Eidelberg, D., During, M.J., 2007. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet 369, 2097–2105.
Khoo, M.L., Tao, H., Meedeniya, A.C., Mackay-Sim, A., Ma, D.D., 2011. Transplantation of neuronal-primed human bone marrow mesenchymal stem cells in hemiparkinsonian rodents. PLoS ONE 6, e19025.
Kim, J.H., Auerbach, J.M., Rodriguez-Gomez, J.A., Velasco, I., Gavin, D., Lumelsky, N., Lee, S.H., Nguyen, J., Sanchez-Pernaute, R., Bankiewicz, K., McKay, R., 2002. Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. Nature 418, 50–56.
Kim, Y.J., Park, H.J., Lee, G., Bang, O.Y., Ahn, Y.H., Joe, E., Kim, H.O., Lee, P.H., 2009. Neuroprotective effects of human mesenchymal stem cells on dopaminergic neurons through anti-inflammatory action. Glia 57, 13–23.
Kishk, N., Abokrysha, N., 2011. Stem cell in neurological disorders. In: Gholamrezanezhad, A. (Ed.), Stem Cells in Clinic and Research. In Tech, pp. 363–400.
Kiss, L.E., Ferreira, H.S., Torrao, L., Bonifacio, M.J., Palma, P.N., Soares-da-Silva, P., Learmonth, D.A., 2010. Discovery of a long-acting, peripherally selective inhibitor of catechol-O-methyltransferase. J. Med. Chem. 53, 3396–3411.
Kitagawa, M., Murata, J., Uesugi, H., Kikuchi, S., Saito, H., Tashiro, K., Sawamura, Y., 2005. Two-year follow-up of chronic stimulation of the posterior subthalamic white matter for tremor-dominant Parkinson's disease. Neurosurgery 56, 281–289 (discussion 281–289).
Knudsen Gerber, D.S., 2011. Selegiline and rasagiline: twins or distant cousins? Consult. Pharm. 26, 48–51.
Koller, W.C., 2003. Handbook of Parkinson's Disease. Marcel Dekker, New York.
Kordower, J.H., Chu, Y., Hauser, R.A., Freeman, T.B., Olanow, C.W., 2008. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat. Med. 14, 504–506.
Kordower, J.H., Herzog, C.D., Dass, B., Bakay, R.A., Stansell III, J., Gasmi, M., Bartus, R. T., 2006. Delivery of neurturin by AAV2 (CERE-120)-mediated gene transfer provides structural and functional neuroprotection and neurorestoration in MPTP-treated monkeys. Ann. Neurol. 60, 706–715.
Kordower, J.H., Olanow, C.W., Dodiya, H.B., Chu, Y., Beach, T.G., Adler, C.H., Halliday, G.M., Bartus, R.T., 2013. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. Brain 136, 2419–2431.
Kordower, J.H., Rosenstein, J.M., Collier, T.J., Burke, M.A., Chen, E.Y., Li, J.M., Martel, L., Levey, A.E., Mufson, E.J., Freeman, T.B., Olanow, C.W., 1996. Functional fetal nigral grafts in a patient with Parkinson's disease: chemoanatomic, ultrastructural, and metabolic studies. J. Comp. Neurol. 370, 203–230.
Kotzbauer, P.T., Lampe, P.A., Heuckeroth, R.O., Golden, J.P., Creedon, D.J., Johnson Jr., E.M., Milbrandt, J., 1996. Neurturin, a relative of glial-cell-line-derived neurotrophic factor. Nature 384, 467–470.
Lang, A.E., Gill, S., Patel, N.K., Lozano, A., Nutt, J.G., Penn, R., Brooks, D.J., Hotton, G., Moro, E., Heywood, P., Brodsky, M.A., Burchiel, K., Kelly, P., Dalvi, A., Scott, B.,

Stacy, M., Turner, D., Wooten, V.G., Elias, W.J., Laws, E.R., Dhawan, V., Stoessl, A.J., Matcham, J., Coffey, R.J., Traub, M., 2006. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. Ann. Neurol. 59, 459–466.
Lang, A.E., Lees, A., 2002. Management of Parkinson's disease: an evidence-based review. Mov. Disord. 17 (Suppl. 4), S1–S166.
Larsen, J.P., Worm-Petersen, J., Siden, A., Gordin, A., Reinikainen, K., Leinonen, M., 2003. The tolerability and efficacy of entacapone over 3 years in patients with Parkinson's disease. Eur. J. Neurol. 10, 137–146.
Lee, B., Lee, H., Nam, Y.R., Oh, J.H., Cho, Y.H., Chang, J.W., 2005. Enhanced expression of glutamate decarboxylase 65 improves symptoms of rat parkinsonian models. Gene Ther. 12, 1215–1222.
Levy, Y.S., Bahat-Stroomza, M., Barzilay, R., Burshtein, A., Bulvik, S., Barhum, Y., Panet, H., Melamed, E., Offen, D., 2008. Regenerative effect of neural-induced human mesenchymal stromal cells in rat models of Parkinson's disease. Cytotherapy 10, 340–352.
LeWitt, P.A., Rezai, A.R., Leehey, M.A., Ojemann, S.G., Flaherty, A.W., Eskandar, E.N., Kostyk, S.K., Thomas, K., Sarkar, A., Siddiqui, M.S., Tatter, S.B., Schwalb, J.M., Poston, K.L., Henderson, J.M., Kurlan, R.M., Richard, I.H., Van Meter, L., Sapan, C. V., During, M.J., Kaplitt, M.G., Feigin, A., 2011. AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial. Lancet Neurol. 10, 309–319.
Li, J.Y., Englund, E., Holton, J.L., Soulet, D., Hagell, P., Lees, A.J., Lashley, T., Quinn, N.P., Rehncrona, S., Bjorklund, A., Widner, H., Revesz, T., Lindvall, O., Brundin, P., 2008. Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat. Med. 14, 501–503.
Li, Y., Chen, J., Chen, X.G., Wang, L., Gautam, S.C., Xu, Y.X., Katakowski, M., Zhang, L.J., Lu, M., Janakiraman, N., Chopp, M., 2002. Human marrow stromal cell therapy for stroke in rat: neurotrophins and functional recovery. Neurology 59, 514–523.
Lian, Q., Zhang, Y., Zhang, J., Zhang, H.K., Wu, X., Zhang, Y., Lam, F.F., Kang, S., Xia, J.C., Lai, W.H., Au, K.W., Chow, Y.Y., Siu, C.W., Lee, C.N., Tse, H.F., 2010. Functional mesenchymal stem cells derived from human induced pluripotent stem cells attenuate limb ischemia in mice. Circulation 121, 1113–1123.
Lin, Y.C., Ko, T.L., Shih, Y.H., Lin, M.Y., Fu, T.W., Hsiao, H.S., Hsu, J.Y., Fu, Y.S., 2011. Human umbilical mesenchymal stem cells promote recovery after ischemic stroke. Stroke 42, 2045–2053.
Lindvall, O., Brundin, P., Widner, H., Rehncrona, S., Gustavii, B., Frackowiak, R., Leenders, K.L., Sawle, G., Rothwell, J.C., Marsden, C.D., et al., 1990. Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science 247, 574–577.
Liu, J., Song, L., Jiang, C., Liu, Y., George, J., Ye, H., Cui, Z., 2012. Electrophysiological properties and synaptic function of mesenchymal stem cells during neurogenic differentiation – a mini-review. Int. J. Artif. Organs 35, 323–337.
Lopatina, T., Kalinina, N., Karagyaur, M., Stambolsky, D., Rubina, K., Revischin, A., Pavlova, G., Parfyonova, Y., Tkachuk, V., 2011. Adipose-derived stem cells stimulate regeneration of peripheral nerves: BDNF secreted by these cells promotes nerve healing and axon growth de novo. PLoS ONE 6, e17899.
Luo, J., Kaplitt, M.G., Fitzsimons, H.L., Zuzga, D.S., Liu, Y., Oshinsky, M.L., During, M.J., 2002. Subthalamic GAD gene therapy in a Parkinson's disease rat model. Science 298, 425–429.
Maranis, S., Stamatis, D., Tsironis, C., Konitsiotis, S., 2012. Investigation of the antidyskinetic site of action of metabotropic and ionotropic glutamate receptor antagonists. Intracerebral infusions in 6-hydroxydopamine-lesioned rats with levodopa-induced dyskinesia. Eur. J. Pharmacol. 683, 71–77.
Marconi, S., Zwingers, T., 2014. Comparative efficacy of selegiline versus rasagiline in the treatment of early Parkinson's disease. Eur. Rev. Med. Pharmacol. Sci. 18, 1879–1882.
Marino, M.J., Conn, P.J., 2006. Glutamate-based therapeutic approaches: allosteric modulators of metabotropic glutamate receptors. Curr. Opin. Pharmacol. 6, 98–102.
Marks Jr., W.J., Bartus, R.T., Siffert, J., Davis, C.S., Lozano, A., Boulis, N., Vitek, J., Stacy, M., Turner, D., Verhagen, L., Bakay, R., Watts, R., Guthrie, B., Jankovic, J., Simpson, R., Tagliati, M., Alterman, R., Stern, M., Baltuch, G., Starr, P.A., Larson, P.S., Ostrem, J.L., Nutt, J., Kieburtz, K., Kordower, J.H., Olanow, C.W., 2010. Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. Lancet Neurol. 9, 1164–1172.
Marks Jr., W.J., Ostrem, J.L., Verhagen, L., Starr, P.A., Larson, P.S., Bakay, R.A., Taylor, R., Cahn-Weiner, D.A., Stoessl, A.J., Olanow, C.W., Bartus, R.T., 2008. Safety and tolerability of intraputaminal delivery of CERE-120 (adeno-associated virus serotype 2-neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial. Lancet Neurol. 7, 400–408.
Martinez Banaclocha, M., 2000. N-acetylcysteine elicited increase in complex I activity in synaptic mitochondria from aged mice: implications for treatment of Parkinson's disease. Brain Res. 859, 173–175.
Martinez-Banaclocha, M.A., 2012. N-acetyl-cysteine in the treatment of Parkinson's disease. What are we waiting for? Med. Hypotheses 79, 8–12.
Maruyama, W., Takahashi, T., Youdim, M., Naoi, M., 2002. The anti-Parkinson drug, rasagiline, prevents apoptotic DNA damage induced by peroxynitrite in human dopaminergic neuroblastoma SH-SY5Y cells. J. Neural Transm. 109, 467–481.
Massano, J., Bhatia, K.P., 2012. Clinical approach to Parkinson's disease: features, diagnosis, and principles of management. Cold Spring Harb. Perspect. Med. 2, a008870.
Mathieu, P., Roca, V., Gamba, C., Del Pozo, A., Pitossi, F., 2012. Neuroprotective effects of human umbilical cord mesenchymal stromal cells in an immunocompetent animal model of Parkinson's disease. J. Neuroimmunol. 246, 43–50.
McCoy, M.K., Martinez, T.N., Ruhn, K.A., Wrage, P.C., Keefer, E.W., Botterman, B.R., Tansey, K.E., Tansey, M.G., 2008. Autologous transplants of Adipose-Derived Adult Stromal (ADAS) cells afford dopaminergic neuroprotection in a model of Parkinson's disease. Exp. Neurol. 210, 14–29.
Meirelles Lda, S., Fontes, A.M., Covas, D.T., Caplan, A.I., 2009. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. Cytokine Growth Factor Rev. 20, 419–427.
Meyer, A.K., Maisel, M., Hermann, A., Stirl, K., Storch, A., 2010. Restorative approaches in Parkinson's disease: which cell type wins the race? J. Neurol. Sci. 289, 93–103.
Meyers, R., 1942. The modification of alternating tremors, rigidity and festination by surgery of the basal ganglia. Res. Publ. Nerv. Ment. Dis. Proc. 21, 602–665.
Meyers, R., 1951. Surgical experiments in the therapy of certain 'extrapyramidal' diseases: a current evaluation. Acta Psychiatr. Neurol. Suppl. 67, 1–42.
Mitchell, K.E., Weiss, M.L., Mitchell, B.M., Martin, P., Davis, D., Morales, L., Helwig, B., Beerenstrauch, M., Abou-Easa, K., Hildreth, T., Troyer, D., Medicetty, S., 2003. Matrix cells from Wharton's jelly form neurons and glia. Stem Cells 21, 50–60.
Monti, D.A., Zabrecky, G., Kremens, D., Liang, T.W., Wintering, N.A., Cai, J., Wei, X., Bazzan, A.J., Zhong, L., Bowen, B., Intenzo, C.M., Iacovitti, L., Newberg, A.B., 2016. N-acetyl cysteine may support dopamine neurons in Parkinson's disease: preliminary clinical and cell line data. PLoS ONE 11, e0157602.
Moro, E., Lozano, A.M., Pollak, P., Agid, Y., Rehncrona, S., Volkmann, J., Kulisevsky, J., Obeso, J.A., Albanese, A., Hariz, M.I., Quinn, N.P., Speelman, J.D., Benabid, A.L., Fraix, V., Mendes, A., Welter, M.L., Houeto, J.L., Cornu, P., Dormont, D., Tornqvist, A.L., Ekberg, R., Schnitzler, A., Timmermann, L., Wojtecki, L., Gironell, A., Rodriguez-Oroz, M.C., Guridi, J., Bentivoglio, A.R., Contarino, M.F., Romito, L., Scerrati, M., Janssens, M., Lang, A.E., 2010. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov. Disord. 25, 578–586.
Muller, T., 2016. Emerging approaches in Parkinson's disease – adjunctive role of safinamide. Ther. Clin. Risk Manag. 12, 1151–1160.
Muller, T., Buttner, T., Gholipour, A.F., Kuhn, W., 2003. Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease. Neurosci. Lett. 341, 201–204.
Munoz-Elias, G., Marcus, A.J., Coyne, T.M., Woodbury, D., Black, I.B., 2004. Adult bone marrow stromal cells in the embryonic brain: engraftment, migration, differentiation, and long-term survival. J. Neurosci. 24, 4585–4595.
Nandhagopal, R., McKeown, M.J., Stoessl, A.J., 2008. Functional imaging in Parkinson disease. Neurology 70, 1478–1488.
Navntoft, C.A., Dreyer, J.K., 2016. How compensation breaks down in Parkinson's disease: insights from modeling of denervated striatum. Mov. Disord. 31, 280–289.
Neuhuber, B., Timothy Himes, B., Shumsky, J.S., Gallo, G., Fischer, I., 2005. Axon growth and recovery of function supported by human bone marrow stromal cells in the injured spinal cord exhibit donor variations. Brain Res. 1035, 73–85.
Nicoletti, F., Bockaert, J., Collingridge, G.L., Conn, P.J., Ferraguti, F., Schoepp, D.D., Wroblewski, J.T., Pin, J.P., 2011. Metabotropic glutamate receptors: from the workbench to the bedside. Neuropharmacology 60, 1017–1041.
Niswender, C.M., Johnson, K.A., Weaver, C.D., Jones, C.K., Xiang, Z., Luo, Q., Rodriguez, A.L., Marlo, J.E., de Paulis, T., Thompson, A.D., Days, E.L., Nalywajko, T., Austin, C. A., Williams, M.B., Ayala, J.E., Williams, R., Lindsley, C.W., Conn, P.J., 2008. Discovery, characterization, and antiparkinsonian effect of novel positive allosteric modulators of metabotropic glutamate receptor 4. Mol. Pharmacol. 74, 1345–1358.
Nutt, J.G., Burchiel, K.J., Comella, C.L., Jankovic, J., Lang, A.E., Laws Jr., E.R., Lozano, A. M., Penn, R.D., Simpson Jr., R.K., Stacy, M., Wooten, G.F., 2003. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. Neurology 60, 69–73.
Nutt, J.G., Woodward, W.R., Beckner, R.M., Stone, C.K., Berggren, K., Carter, J.H., Gancher, S.T., Hammerstad, J.P., Gordin, A., 1994. Effect of peripheral catechol-O-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. Neurology 44, 913–919.
Obeso, J.A., Olanow, C.W., Nutt, J.G., 2000. Levodopa motor complications in Parkinson's disease. Trends Neurosci. 23, S2–S7.
Offen, D., Barhum, Y., Levy, Y.S., Burshtein, A., Panet, H., Cherlow, T., Melamed, E., 2007. Intrastriatal transplantation of mouse bone marrow-derived stem cells improves motor behavior in a mouse model of Parkinson's disease. J. Neural Transm. Suppl. 72, 133–143.
Okun, M.S., 2013. Erratum: A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort: Clinical article. J. Neurosurg. 113, 1086.
Okun, M.S., Fernandez, H.H., Wu, S.S., Kirsch-Darrow, L., Bowers, D., Bova, F., Suelter, M., Jacobson, C.E.t., Wang, X., Gordon Jr., C.W., Zeilman, P., Romrell, J., Martin, P., Ward, H., Rodriguez, R.L., Foote, K.D., 2009. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. Ann. Neurol. 65, 586–595.
Olanow, C.W., Brundin, P., 2013. Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder? Mov. Disord. 28, 31–40.
Olanow, C.W., Goetz, C.G., Kordower, J.H., Stoessl, A.J., Sossi, V., Brin, M.F., Shannon, K.M., Nauert, G.M., Perl, D.P., Godbold, J., Freeman, T.B., 2003. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann. Neurol. 54, 403–414.
Olanow, C.W., Hauser, R.A., Jankovic, J., Langston, W., Lang, A., Poewe, W., Tolosa, E., Stocchi, F., Melamed, E., Eyal, E., Rascol, O., 2008a. A randomized, double-blind, placebo-controlled, delayed start study to assess rasagiline as a disease

modifying therapy in Parkinson's disease (the ADAGIO study): rationale, design, and baseline characteristics. Mov. Disord. 23, 2194–2201.
Olanow, C.W., Kieburtz, K., Schapira, A.H., 2008b. Why have we failed to achieve neuroprotection in Parkinson's disease? Ann. Neurol. 64 (Suppl. 2), S101–S110.
Olanow, C.W., Rascol, O., Hauser, R., Feigin, P.D., Jankovic, J., Lang, A., Langston, W., Melamed, E., Poewe, W., Stocchi, F., Tolosa, E., 2009a. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N. Engl. J. Med. 361, 1268–1278.
Olanow, C.W., Stern, M.B., Sethi, K., 2009b. The scientific and clinical basis for the treatment of Parkinson disease (2009). Neurology 72, S1–S136.
Olanow, C.W., Watts, R.L., Koller, W.C., 2001. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology 56, S1–S88.
Onofrj, M., Bonanni, L., Thomas, A., 2008. An expert opinion on safinamide in Parkinson's disease. Expert Opin. Investig. Drugs 17, 1115–1125.
Paek, S.B., Min, H.K., Kim, I., Knight, E.J., Baek, J.J., Bieber, A.J., Lee, K.H., Chang, S.Y., 2015. Frequency-dependent functional neuromodulatory effects on the motor network by ventral lateral thalamic deep brain stimulation in swine. Neuroimage 105, 181–188.
Pandey, S., 2012. Parkinson's disease: recent advances. J. Assoc. Physicians India 60, 30–32.
Parish, C.L., Castelo-Branco, G., Rawal, N., Tonnesen, J., Sorensen, A.T., Salto, C., Kokaia, M., Lindvall, O., Arenas, E., 2008. Wnt5a-treated midbrain neural stem cells improve dopamine cell replacement therapy in parkinsonian mice. J. Clin. Invest. 118, 149–160.
Park, H.J., Shin, J.Y., Lee, B.R., Kim, H.O., Lee, P.H., 2012. Mesenchymal stem cells augment neurogenesis in the subventricular zone and enhance differentiation of neural precursor cells into dopaminergic neurons in the substantia nigra of a parkinsonian model. Cell Transplant. 21, 1629–1640.
Park, S., Lee, K.S., Lee, Y.J., Shin, H.A., Cho, H.Y., Wang, K.C., Kim, Y.S., Lee, H.T., Chung, K.S., Kim, E.Y., Lim, J., 2004. Generation of dopaminergic neurons in vitro from human embryonic stem cells treated with neurotrophic factors. Neurosci. Lett. 359, 99–103.
Parkinson, J., 1817. An Essay on the Shaking Palsy. Whittingham & Rowland, London.
Parkinson Study, G., 2004. The safety and tolerability of a mixed lineage kinase inhibitor (CEP-1347) in PD. Neurology 62, 330–332.
Parkinson Study Group, P.I., 2007. Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson disease. Neurology 69, 1480–1490.
Parkinson Study Group, Q.E.I., Beal, M.F., Oakes, D., Shoulson, I., Henchcliffe, C., Galpern, W.R., Haas, R., Juncos, J.L., Nutt, J.G., Voss, T.S., Ravina, B., Shults, C.M., Helles, K., Snively, V., Lew, M.F., Griebner, B., Watts, A., Gao, S., Pourcher, E., Bond, L., Kompoliti, K., Agarwal, P., Sia, C., Jog, M., Cole, L., Sultana, M., Kurlan, R., Richard, I., Deeley, C., Waters, C.H., Figueroa, A., Arkun, A., Brodsky, M., Ondo, W. G., Hunter, C.B., Jimenez-Shahed, J., Palao, A., Miyasaki, J.M., So, J., Tetrud, J., Reys, L., Smith, K., Singer, C., Blenke, A., Russell, D.S., Cotto, C., Friedman, J.H., Lannon, M., Zhang, L., Drasby, E., Kumar, R., Subramanian, T., Ford, D.S., Grimes, D.A., Cote, D., Conway, J., Siderowf, A.D., Evatt, M.L., Sommerfeld, B., Lieberman, A.N., Okun, M.S., Rodriguez, R.L., Merritt, S., Swartz, C.L., Martin, W.R., King, P., Stover, N., Guthrie, S., Watts, R.L., Ahmed, A., Fernandez, H.H., Winters, A., Mari, Z., Dawson, T.M., Dunlop, B., Feigin, A.S., Shannon, B., Nirenberg, M.J., Ogg, M., Ellias, S.A., Thomas, C.A., Frei, K., Bodis-Wollner, I., Glazman, S., Mayer, T., Hauser, R.A., Pahwa, R., Langhammer, A., Ranawaya, R., Derwent, L., Sethi, K.D., Farrow, B., Prakash, R., Litvan, I., Robinson, A., Sahay, A., Gartner, M., Hinson, V.K., Markind, S., Pelikan, M., Perlmutter, J.S., Hartlein, J., Molho, E., Evans, S., Adler, C. H., Duffy, A., Lind, M., Elmer, L., Davis, K., Spears, J., Wilson, S., Leehey, M.A., Hermanowicz, N., Niswonger, S., Shill, H.A., Obradov, S., Rajput, A., Cowper, M., Lessig, S., Song, D., Fontaine, D., Zadikoff, C., Williams, K., Blindauer, K.A., Bergholte, J., Propsom, C.S., Stacy, M.A., Field, J., Mihaila, D., Chilton, M., Uc, E.Y., Sieren, J., Simon, D.K., Kraics, L., Silver, A., Boyd, J.T., Hamill, R.W., Ingvoldstad, C., Young, J., Thomas, K., Kostyk, S.K., Wojcieszek, J., Pfeiffer, R.F., Panisset, M., Beland, M., Reich, S.G., Cines, M., Zappala, N., Rivest, J., Zweig, R., Lumina, L.P., Hilliard, C.L., Grill, S., Kellermann, M., Tuite, P., Rolandelli, S., Kang, U.J., Young, J., Rao, J., Cook, M.M., Severt, L., Boyar, K., 2014. A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: no evidence of benefit. JAMA Neurol. 71, 543–552.
Parkinson Study Group, 1989. DATATOP: a multicenter controlled clinical trial in early Parkinson's disease. Arch. Neurol. 46, 1052–1060.
Parkinson Study Group, 1997. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann. Neurol. 42, 747–755.
Parkinson Study Group, 2000. Pramipexole vs. levodopa as initial treatment for Parkinson disease: a randomized controlled trial. JAMA 284, 1931–1938.
Parkinson Study Group, 2002. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. Arch. Neurol. 59, 1937–1943.
Pereira, E.A., Aziz, T.Z., 2006. Surgical insights into Parkinson's disease. J. R. Soc. Med. 99, 238–244.
Peretz, C., Segev, H., Rozani, V., Gurevich, T., El-Ad, B., Tsamir, J., Giladi, N., 2016. Comparison of selegiline and rasagiline therapies in Parkinson disease: a real-life study. Clin. Neuropharmacol. 39, 227–231.
Perez-Lloret, S., Rascol, O., 2016. The safety and efficacy of safinamide mesylate for the treatment of Parkinson's disease. Expert Rev. Neurother. 16, 245–258.
Perlow, M.J., Freed, W.J., Hoffer, B.J., Seiger, A., Olson, L., Wyatt, R.J., 1979. Brain grafts reduce motor abnormalities produced by destruction of nigrostriatal dopamine system. Science 204, 643–647.
Perrier, A.L., Tabar, V., Barberi, T., Rubio, M.E., Bruses, J., Topf, N., Harrison, N.L., Studer, L., 2004. Derivation of midbrain dopamine neurons from human embryonic stem cells. Proc. Natl. Acad. Sci. U. S. A. 101, 12543–12548.
Perrone-Capano, C., Di Porzio, U., 2000. Genetic and epigenetic control of midbrain dopaminergic neuron development. Int. J. Dev. Biol. 44, 679–687.
Pfeiffer, R.F., Gutmann, L., Hull Jr., K.L., Bottini, P.B., Sherry, J.H., 2007. Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease. Parkinsonism Relat. Disord. 13, 93–100.
Pfisterer, U., Kirkeby, A., Torper, O., Wood, J., Nelander, J., Dufour, A., Bjorklund, A., Lindvall, O., Jakobsson, J., Parmar, M., 2011. Direct conversion of human fibroblasts to dopaminergic neurons. Proc. Natl. Acad. Sci. U. S. A. 108, 10343–10348.
Phinney, D.G., Prockop, D.J., 2007. Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair – current views. Stem Cells 25, 2896–2902.
Plaha, P., Ben-Shlomo, Y., Patel, N.K., Gill, S.S., 2006. Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. Brain 129, 1732–1747.
Plaha, P., Gill, S.S., 2005. Bilateral deep brain stimulation of the pedunculopontine nucleus for Parkinson's disease. Neuroreport 16, 1883–1887.
Poewe, W.H., Deuschl, G., Gordin, A., Kultalahti, E.R., Leinonen, M., 2002. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). Acta Neurol. Scand. 105, 245–255.
Politis, M., Lindvall, O., 2012a. Clinical application of stem cell therapy in Parkinson's disease. BMC Med. 10, 1.
Politis, M., Lindvall, O., 2012b. Clinical application of stem cell therapy in Parkinson's disease. BMC Med. 10, 1–7.
Pope-Coleman, A., Tinker, J.P., Schneider, J.S., 2000. Effects of GM1 ganglioside treatment on pre- and postsynaptic dopaminergic markers in the striatum of parkinsonian monkeys. Synapse 36, 120–128.
Rascol, O., 2009. Disease-modification" trials in Parkinson disease: target populations, endpoints and study design. Neurology 72, S51–S58.
Rascol, O., Brooks, D.J., Korczyn, A.D., De Deyn, P.P., Clarke, C.E., Lang, A.E., 2000. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N. Engl. J. Med. 342, 1484–1491.
Rascol, O., Lozano, A., Stern, M., Poewe, W., 2011. Milestones in Parkinson's disease therapeutics. Mov. Disord. 26, 1072–1082.
Rinne, U.K., Larsen, J.P., Siden, A., Worm-Petersen, J., 1998. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. Neurology 51, 1309–1314.
Rocha, J.F., Falcao, A., Santos, A., Pinto, R., Lopes, N., Nunes, T., Wright, L.C., Vaz-da-Silva, M., Soares-da-Silva, P., 2014. Effect of opicapone and entacapone upon levodopa pharmacokinetics during three daily levodopa administrations. Eur. J. Clin. Pharmacol. 70, 1059–1071.
Rodnitzky, R.L., 2012. Upcoming treatments in Parkinson's disease, including gene therapy. Parkinsonism Relat. Disord. 18 (Suppl. 1), S37–S40.
Rowland, N.C., Starr, P.A., Larson, P.S., Ostrem, J.L., Marks Jr., W.J., Lim, D.A., 2015. Combining cell transplants or gene therapy with deep brain stimulation for Parkinson's disease. Mov. Disord. 30, 190–195.
Roy, N.S., Cleren, C., Singh, S.K., Yang, L., Beal, M.F., Goldman, S.A., 2006. Functional engraftment of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes. Nat. Med. 12, 1259–1268.
Sackeim, H.A., George, M.S., 2008. Brain stimulation-basic, translational, and clinical research in neuromodulation: why a new journal? Brain Stimul. 1, 4–6.
Sadan, O., Bahat-Stromza, M., Barhum, Y., Levy, Y.S., Pisnevsky, A., Peretz, H., Ilan, A. B., Bulvik, S., Shemesh, N., Krepel, D., Cohen, Y., Melamed, E., Offen, D., 2009. Protective effects of neurotrophic factor-secreting cells in a 6-OHDA rat model of Parkinson disease. Stem Cells Dev. 18, 1179–1190.
Salama, M., Eldakroory, S.A., Eltantawy, D., Ghanem, A.A., Elghaffar, H.A., Elhusseiny, M., Elhak, S.G., 2012. Regenerative effects of umbilical cord matrix cells (UCMCs) in a rodent model of rotenone neurotoxicity. Environ. Toxicol. Pharmacol. 34, 338–344.
Salgado, A.J., Oliveira, J.T., Pedro, A.J., Reis, R.L., 2006. Adult stem cells in bone and cartilage tissue engineering. Curr. Stem Cell Res. Ther. 1, 345–364.
Sanchez-Danes, A., Richaud-Patin, Y., Carballo-Carbajal, I., Jimenez-Delgado, S., Caig, C., Mora, S., Di Guglielmo, C., Ezquerra, M., Patel, B., Giralt, A., Canals, J.M., Memo, M., Alberch, J., Lopez-Barneo, J., Vila, M., Cuervo, A.M., Tolosa, E., Consiglio, A., Raya, A., 2012. Disease-specific phenotypes in dopamine neurons from human iPS-based models of genetic and sporadic Parkinson's disease. EMBO Mol. Med. 4, 380–395.
Sanchez-Pernaute, R., Studer, L., Bankiewicz, K.S., Major, E.O., McKay, R.D., 2001. In vitro generation and transplantation of precursor-derived human dopamine neurons. J. Neurosci. Res. 65, 284–288.
Sawamoto, K., Nakao, N., Kakishita, K., Ogawa, Y., Toyama, Y., Yamamoto, A., Yamaguchi, M., Mori, K., Goldman, S.A., Itakura, T., Okano, H., 2001. Generation of dopaminergic neurons in the adult brain from mesencephalic precursor cells labeled with a nestin-GFP transgene. J. Neurosci. 21, 3895–3903.
Schapira, A.H., 2005. Present and future drug treatment for Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 76, 1472–1478.
Schneider, J.S., Cambi, F., Gollomp, S.M., Kuwabara, H., Brasic, J.R., Leiby, B., Sendek, S., Wong, D.F., 2015. GM1 ganglioside in Parkinson's disease: pilot study of effects on dopamine transporter binding. J. Neurol. Sci. 356, 118–123.
Schneider, J.S., Gollomp, S.M., Sendek, S., Colcher, A., Cambi, F., Du, W., 2013. A randomized, controlled, delayed start trial of GM1 ganglioside in treated Parkinson's disease patients. J. Neurol. Sci. 324, 140–148.

Schneider, J.S., Kean, A., DiStefano, L., 1995. GM1 ganglioside rescues substantia nigra pars compacta neurons and increases dopamine synthesis in residual nigrostriatal dopaminergic neurons in MPTP-treated mice. J. Neurosci. Res. 42, 117–123.
Schneider, J.S., Roeltgen, D.P., Mancall, E.L., Chapas-Crilly, J., Rothblat, D.S., Tatarian, G.T., 1998. Parkinson's disease: improved function with GM1 ganglioside treatment in a randomized placebo-controlled study. Neurology 50, 1630–1636.
Schneider, J.S., Sendek, S., Daskalakis, C., Cambi, F., 2010. GM1 ganglioside in Parkinson's disease: results of a five year open study. J. Neurol. Sci. 292, 45–51.
Schupbach, W.M., Chastan, N., Welter, M.L., Houeto, J.L., Mesnage, V., Bonnet, A.M., Czernecki, V., Maltete, D., Hartmann, A., Mallet, L., Pidoux, B., Dormont, D., Navarro, S., Cornu, P., Mallet, A., Agid, Y., 2005. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. J. Neurol. Neurosurg. Psychiatry 76, 1640–1644.
Schwalb, J.M., Hamani, C., 2008. The history and future of deep brain stimulation. Neurotherapeutics 5, 3–13.
Schwarz, S.C., Wittlinger, J., Schober, R., Storch, A., Schwarz, J., 2006. Transplantation of human neural precursor cells in the 6-OHDA lesioned rats: effect of immunosuppression with cyclosporine A. Parkinsonism Relat. Disord. 12, 302–308.
Scott, L.J., 2016. Opicapone: a review in Parkinson's disease. Drugs 76, 1293–1300.
Seet, R.C., Lim, E.C., Tan, J.J., Quek, A.M., Chow, A.W., Chong, W.L., Ng, M.P., Ong, C.N., Halliwell, B., 2014. Does high-dose coenzyme Q10 improve oxidative damage and clinical outcomes in Parkinson's disease? Antioxid. Redox Signal. 21, 211–217.
Seo, J.H., Cho, S.R., 2012. Neurorestoration induced by mesenchymal stem cells: potential therapeutic mechanisms for clinical trials. Yonsei Med. J. 53, 1059–1067.
Shamekh, R., Saporta, S., Cameron, D.F., Willing, A.E., Sanberg, C.D., Johe, K., Sanberg, P.R., 2008. Effects of Sertoli cell-conditioned medium on ventral midbrain neural stem cells: a preliminary report. Neurotox. Res. 13, 241–246.
Sherer, T.B., Fiske, B.K., Svendsen, C.N., Lang, A.E., Langston, J.W., 2006. Crossroads in GDNF therapy for Parkinson's disease. Mov. Disord. 21, 136–141.
Shetty, P., Ravindran, G., Sarang, S., Thakur, A.M., Rao, H.S., Viswanathan, C., 2009. Clinical grade mesenchymal stem cells transdifferentiated under xenofree conditions alleviates motor deficiencies in a rat model of Parkinson's disease. Cell Biol. Int. 33, 830–838.
Shetty, P., Thakur, A.M., Viswanathan, C., 2013. Dopaminergic cells, derived from a high efficiency differentiation protocol from umbilical cord derived mesenchymal stem cells, alleviate symptoms in a Parkinson's disease rodent model. Cell Biol. Int. 37, 167–180.
Shintani, A., Nakao, N., Kakishita, K., Itakura, T., 2007. Protection of dopamine neurons by bone marrow stromal cells. Brain Res. 1186, 48–55.
Shulman, L.M., Taback, R.L., Bean, J., Weiner, W.J., 2001. Comorbidity of the nonmotor symptoms of Parkinson's disease. Mov. Disord. 16, 507–510.
Shulman, L.M., Taback, R.L., Rabinstein, A.A., Weiner, W.J., 2002. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat. Disord. 8, 193–197.
Shults, C.W., Oakes, D., Kieburtz, K., Beal, M.F., Haas, R., Plumb, S., Juncos, J.L., Nutt, J., Shoulson, I., Carter, J., Kompoliti, K., Perlmutter, J.S., Reich, S., Stern, M., Watts, R. L., Kurlan, R., Molho, E., Harrison, M., Lew, M., Parkinson Study, G., 2002. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch. Neurol. 59, 1541–1550.
Simon-Sanchez, J., Schulte, C., Bras, J.M., Sharma, M., Gibbs, J.R., Berg, D., Paisan-Ruiz, C., Lichtner, P., Scholz, S.W., Hernandez, D.G., Kruger, R., Federoff, M., Klein, C., Goate, A., Perlmutter, J., Bonin, M., Nalls, M.A., Illig, T., Gieger, C., Houlden, H., Steffens, M., Okun, M.S., Racette, B.A., Cookson, M.R., Foote, K.D., Fernandez, H. H., Traynor, B.J., Schreiber, S., Arepalli, S., Zonozi, R., Gwinn, K., van der Brug, M., Lopez, G., Chanock, S.J., Schatzkin, A., Park, Y., Hollenbeck, A., Gao, J., Huang, X., Wood, N.W., Lorenz, D., Deuschl, G., Chen, H., Riess, O., Hardy, J.A., Singleton, A. B., Gasser, T., 2009. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat. Genet. 41, 1308–1312.
Smith, Y., Wichmann, T., Factor, S.A., DeLong, M.R., 2012. Parkinson's disease therapeutics: new developments and challenges since the introduction of levodopa. Neuropsychopharmacology 37, 213–246.
Soldner, F., Hockemeyer, D., Beard, C., Gao, Q., Bell, G.W., Cook, E.G., Hargus, G., Blak, A., Cooper, O., Mitalipova, M., Isacson, O., Jaenisch, R., 2009. Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors. Cell 136, 964–977.
Somoza, R., Juri, C., Baes, M., Wyneken, U., Rubio, F.J., 2010. Intranigral transplantation of epigenetically induced BDNF-secreting human mesenchymal stem cells: implications for cell-based therapies in Parkinson's disease. Biol. Blood Marrow Transplant. 16, 1530–1540.
Soulas, T., Gurruchaga, J.M., Palfi, S., Cesaro, P., Nguyen, J.P., Fenelon, G., 2008. Attempted and completed suicides after subthalamic nucleus stimulation for Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 79, 952–954.
Stocchi, F., Arnold, G., Onofrj, M., Kwiecinski, H., Szczudlik, A., Thomas, A., Bonuccelli, U., Van Dijk, A., Cattaneo, C., Sala, P., Fariello, R.G., Safinamide Parkinson's Study, G., 2004. Improvement of motor function in early Parkinson disease by safinamide. Neurology 63, 746–748.
Stocchi, F., Torti, M., 2016. Adjuvant therapies for Parkinson's disease: critical evaluation of safinamide. Drug Des. Devel. Ther. 10, 609–618.
Storch, A., Jost, W.H., Vieregge, P., Spiegel, J., Greulich, W., Durner, J., Muller, T., Kupsch, A., Henningsen, H., Oertel, W.H., Fuchs, G., Kuhn, W., Niklowitz, P., Koch, R., Herting, B., Reichmann, H., German Coenzyme, Q.S.G., 2007. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q (10) in Parkinson disease. Arch. Neurol. 64, 938–944.
Storch, A., Paul, G., Csete, M., Boehm, B.O., Carvey, P.M., Kupsch, A., Schwarz, J., 2001. Long-term proliferation and dopaminergic differentiation of human mesencephalic neural precursor cells. Exp. Neurol. 170, 317–325.
Storch, A., Sabolek, M., Milosevic, J., Schwarz, S.C., Schwarz, J., 2004. Midbrain-derived neural stem cells: from basic science to therapeutic approaches. Cell Tissue Res. 318, 15–22.
Stowe, R., Ives, N., Clarke, C.E., Handley, K., Furmston, A., Deane, K., van Hilten, J.J., Wheatley, K., Gray, R., 2011. Meta-analysis of the comparative efficacy and safety of adjuvant treatment to levodopa in later Parkinson's disease. Mov. Disord. 26, 587–598.
Strutt, A.M., Simpson, R., Jankovic, J., York, M.K., 2012. Changes in cognitive-emotional and physiological symptoms of depression following STN-DBS for the treatment of Parkinson's disease. Eur. J. Neurol. 19, 121–127.
Svendsen, C.N., Caldwell, M.A., Shen, J., ter Borg, M.G., Rosser, A.E., Tyers, P., Karmiol, S., Dunnett, S.B., 1997. Long-term survival of human central nervous system progenitor cells transplanted into a rat model of Parkinson's disease. Exp. Neurol. 148, 135–146.
Svendsen, C.N., Clarke, D.J., Rosser, A.E., Dunnett, S.B., 1996. Survival and differentiation of rat and human epidermal growth factor-responsive precursor cells following grafting into the lesioned adult central nervous system. Exp. Neurol. 137, 376–388.
Swistowski, A., Peng, J., Liu, Q., Mali, P., Rao, M.S., Cheng, L., Zeng, X., 2010. Efficient generation of functional dopaminergic neurons from human induced pluripotent stem cells under defined conditions. Stem Cells 28, 1893–1904.
Taba, H.A., Wu, S.S., Foote, K.D., Hass, C.J., Fernandez, H.H., Malaty, I.A., Rodriguez, R. L., Dai, Y., Zeilman, P.R., Jacobson, C.E., Okun, M.S., 2010. A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. J. Neurosurg. 113, 1224–1229.
Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., Yamanaka, S., 2007. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131, 861–872.
Takahashi, K., Yamanaka, S., 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126, 663–676.
Tarazi, F.I., Sahli, Z.T., Wolny, M., Mousa, S.A., 2014. Emerging therapies for Parkinson's disease: from bench to bedside. Pharmacol. Ther. 144, 123–133.
Teixeira, F.G., Carvalho, M.M., Panchalingam, K.M., Rodrigues, A.J., Mendes-Pinheiro, B., Anjo, S., Manadas, B., Behie, L.A., Sousa, N., Salgado, A.J., 2016a. Impact of the secretome of human mesenchymal stem cells on brain structure and animal behavior in a rat model of Parkinson's disease. Stem Cells Transl. Med..
Teixeira, F.G., Carvalho, M.M., Sousa, N., Salgado, A.J., 2013. Mesenchymal stem cells secretome: a new paradigm for central nervous system regeneration? Cell. Mol. Life Sci. 70, 3871–3882.
Teixeira, F.G., Panchalingam, K.M., Assuncao-Silva, R., Serra, S.C., Mendes-Pinheiro, B., Patricio, P., Jung, S., Anjo, S.I., Manadas, B., Pinto, L., Sousa, N., Behie, L.A., Salgado, A.J., 2016b. Modulation of the mesenchymal stem cell secretome using computer-controlled bioreactors: impact on neuronal cell proliferation. Surv. Differ. Sci. Rep. 6, 27791.
Thomas, M.G., Stone, L., Evill, L., Ong, S., Ziman, M., Hool, L., 2011. Bone marrow stromal cells as replacement cells for Parkinson's disease: generation of an anatomical but not functional neuronal phenotype. Transl. Res. 157, 56–63.
Trzaska, K.A., Kuzhikandathil, E.V., Rameshwar, P., 2007. Specification of a dopaminergic phenotype from adult human mesenchymal stem cells. Stem Cells 25, 2797–2808.
Venkataramana, N.K., Kumar, S.K., Balaraju, S., Radhakrishnan, R.C., Bansal, A., Dixit, A., Rao, D.K., Das, M., Jan, M., Gupta, P.K., Totey, S.M., 2010. Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson's disease. Transl. Res. 155, 62–70.
Vierbuchen, T., Ostermeier, A., Pang, Z.P., Kokubu, Y., Sudhof, T.C., Wernig, M., 2010. Direct conversion of fibroblasts to functional neurons by defined factors. Nature 463, 1035–1041.
Wakabayashi, K., Nagai, A., Sheikh, A.M., Shiota, Y., Narantuya, D., Watanabe, T., Masuda, J., Kobayashi, S., Kim, S.U., Yamaguchi, S., 2010. Transplantation of human mesenchymal stem cells promotes functional improvement and increased expression of neurotrophic factors in a rat focal cerebral ischemia model. J. Neurosci. Res. 88, 1017–1025.
Wang, F., Yasuhara, T., Shingo, T., Kameda, M., Tajiri, N., Yuan, W.J., Kondo, A., Kadota, T., Baba, T., Tayra, J.T., Kikuchi, Y., Miyoshi, Y., Date, I., 2010. Intravenous administration of mesenchymal stem cells exerts therapeutic effects on parkinsonian model of rats: focusing on neuroprotective effects of stromal cell-derived factor-1alpha. BMC Neurosci. 11, 1–9.
Wang, Y., Yang, J., Li, H., Wang, X., Zhu, L., Fan, M., 2013. Hypoxia promotes dopaminergic differentiation of mesenchymal stem cells and shows benefits for transplantation in a rat model of Parkinson's disease. PLoS ONE 8, e54296.
Wei, X., Du, Z., Zhao, L., Feng, D., Wei, G., He, Y., Tan, J., Lee, W.H., Hampel, H., Dodel, R., Johnstone, B.H., March, K.L., Farlow, M.R., Du, Y., 2009. IFATS collection: the conditioned media of adipose stromal cells protect against hypoxia-ischemia-induced brain damage in neonatal rats. Stem Cells 27, 478–488.
Weiss, M.L., Medicetty, S., Bledsoe, A.R., Rachakatla, R.S., Choi, M., Merchav, S., Luo, Y., Rao, M.S., Velagaleti, G., Troyer, D., 2006. Human umbilical cord matrix stem cells: preliminary characterization and effect of transplantation in a rodent model of Parkinson's disease. Stem Cells 24, 781–792.
Wenning, G.K., Odin, P., Morrish, P., Rehncrona, S., Widner, H., Brundin, P., Rothwell, J.C., Brown, R., Gustavii, B., Hagell, P., Jahanshahi, M., Sawle, G., Bjorklund, A., Brooks, D.J., Marsden, C.D., Quinn, N.P., Lindvall, O., 1997. Short- and long-term

survival and function of unilateral intrastriatal dopaminergic grafts in Parkinson's disease. Ann. Neurol. 42, 95–107.
Wernig, M., Zhao, J.P., Pruszak, J., Hedlund, E., Fu, D., Soldner, F., Broccoli, V., Constantine-Paton, M., Isacson, O., Jaenisch, R., 2008. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. Proc. Natl. Acad. Sci. U. S. A. 105, 5856–5861.
Wichmann, T., DeLong, M.R., 2016. Deep brain stimulation for movement disorders of basal ganglia origin: restoring function or functionality? Neurotherapeutics 13, 264–283.
Widner, H., Tetrud, J., Rehncrona, S., Snow, B., Brundin, P., Gustavii, B., Bjorklund, A., Lindvall, O., Langston, J.W., 1992. Bilateral fetal mesencephalic grafting in two patients with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). N. Engl. J. Med. 327, 1556–1563.
Wright, K.T., El Masri, W., Osman, A., Roberts, S., Chamberlain, G., Ashton, B.A., Johnson, W.E., 2007. Bone marrow stromal cells stimulate neurite outgrowth over neural proteoglycans (CSPG), myelin associated lipoprotein and Novo-A. Biochem. Biophys. Res. Common. 354, 559–566.
Xin, H., Li, Y., Buller, B., Katakowski, M., Zhang, Y., Wang, X., Shang, X., Zhang, Z.G., Chopp, M., 2012. Exosmic-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. Stem Cells 30, 1556–1564.
Yadav, A., Agarwal, S., Tiwari, S.K., Chaturvedi, R.K., 2014. Mitochondria: prospective targets for neuroprotection in Parkinson's disease. Curr. Pharm. Des. 20, 5558–5573.
Yang, C.C., Shih, Y.H., Ko, M.H., Hsu, S.Y., Cheng, H., Fu, Y.S., 2008a. Transplantation of human umbilical mesenchymal stem cells from Wharton's jelly after complete transaction of the rat spinal cord. PLoS ONE 3, e3336.
Yang, D., Zhang, Z.J., Oldenburg, M., Ayala, M., Zhang, S.C., 2008b. Human embryonic stem cell-derived dopaminergic neurons reverse functional deficit in parkinsonian rats. Stem Cells 26, 55–63.
Yao, Y., Huang, C., Gu, P., Wen, T., 2016. Combined MSC-secreted factors and neural stem cell transplantation promote functional recovery of PD rats. Cell Transplant. 25, 1101–1113.
Yi, B.R., Kim, S.U., Choi, K.C., 2013. Development and application of neural stem cells for treating various human neurological diseases in animal models. Lab. Anima. Res. 29, 131–137.
Zhou, Q., Brown, J., Kanarek, A., Rajagopal, J., Melton, D.A., 2008. In vivo reprogramming of adult pancreatic exocrine cells to beta-cells. Nature 455, 627–632.
Zhou, Y., Sun, M., Li, H., Yan, M., He, Z., Wang, W., Lu, S., 2013a. Recovery of behavioral symptoms in hemi-parkinsonian rhesus monkeys through combined gene and stem cell therapy. Cytotherapy 15, 467–480.
Zhou, Y., Xu, H., Xu, W., Wang, B., Wu, H., Tao, Y., Zhang, B., Wang, M., Mao, F., Yan, Y., Gao, S., Gu, H., Zhu, W., Qian, H., 2013b. Exosomes released by human umbilical cord mesenchymal stem cells protect against capsulation-induced renal oxidative stress and apoptosis in vivo and in vitro. Stem Cell Res. Ther. 4, 1–13.
Zhu, Y.G., Feng, X.M., Abbott, J., Fang, X.H., Hao, Q., Monsel, A., Qu, J.M., Matthay, M. A., Lee, J.W., 2013. Human mesenchymal stem cell microvesicles for treatment of *E. coil* end toxin-induced acute lung injury in mice. Stem Cells 32, 116–125.